FORMULATION DEVELOPMENT OF MEGESTEROL ACETATE, A NOVEL APPROACH TO IMPROVE THERAPEUTIC EFFICACY

A Dissertation submitted to

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY, CHENNAI

In the partial fulfillment of the requirement for

the award of degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted by

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This is to certify that this dissertation entitled **"Formulation Development of Megesterol acetate, A Novel Approach to Improve Therapeutic Efficacy"** submitted by **M. BALAJI RAGUNATH (261211352)** in partial fulfillment of the requirement for the award of degree of Master of Pharmacy in Pharmaceutical Analysis by The Tamil Nadu Dr. M.G.R. Medical University, Chennai, is a bonafide record work done by him during the year 2013 – 2014.

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M.Balaji Ragunath

GLOSSARY OF ABBREVIATIONS

^{o}C	Degree centigrade
FT-IR	Fourier Transform Infra Red
µg	Microgram
nm	Nano metres
mg	Milligram
ml	Millilitres
min	Minutes
hr	Hours
%	Percent/percentage
q.s	Quantity sufficient
rpm	Revolutions per Minute
RH	Relative Humidity
HRT	Hormone replacement therapy
BCS	Biopharmaceutical classification System
SMEDDS	Self microemulsifying drug delivery System
SCF	Super critical fluid
GIT	Gastro Intestinal Tract
T_c	Critical Temperature
T_p	Critical Pressure
CD	Cyclodextrins
CMC	Critical micelle concentration
SDS	Sodium dodecyl sulphate
FNA	Fine needle aspiration

CT	Computerised tomography
MRI	Magnetic resonance imaging
DRE	Digital rectal examination
PEG	Polyethylene glycol

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ABSTRACT

Megesterol acetate a synthetic derivative of naturally occurring steroidal hormone progesterone, used in the treatment of breast cancer. The drug is poorly soluble and thermosensitive. The rate of dissolution and its bioavailability is less. In this investigation an attempt was made to develop novel drug to enhance the dissolution of solid oral formulation of Megesterol acetate using solid dispersion and hydrotropic techniques. The tablets can be prepared using less complicated and less expensive excipients, process, as well as to fulfill better therapeutic action for pharmaceutical use. In the study the approach of hydrotropic technique used hydrotropic agents like sodium acetate, sodium benzoate, sodium citrate and urea. In the solid dispersion technique PEG 6000 is used as a carrier. The dissolution pattern of optimized formulation was compared with Innovator product and it was found to be superior to the Innovator product.

Key words: Megesterol acetate, solid dispersion technique, hydrotropic techniques.

SCOPE AND OBJECT

The last 50 yrs has seen a better understanding of the causes and treatment of breast cancer. Hence, early detection and technology has improved the prognosis of cancer patient to an unprecedented level. Megesterol acetate is a novel synthetic antineoplastic and progestational drug in the treatment of breast cancer. It is a new chemical entity, belongs to BCS class II, which exhibits low aqueous solubility and high membrane permeability that leads to poor bioavailability. To develop the formulation the following challenges need to overcome.

1. Poor solubility
2. Thermal degradation
3. Potent drug
4. Poor stability
5. Long elimination half life
6. Onset of action is slow

Conventional megesterol acetate tablets are practically insoluble in water and have slow onset of action and poor bioavailability therefore cannot give effective therapy. Hence I have designed. Formulation development of megesterol acetate immediate release tablets provide following benefits;

1. Megesterol acetate has been to be effective therapy for the treatment of breast and prostate cancer.
2. Improvement of bioavailability, avoidance of tissue accumulation.
3. Gives assurance for long term stability.
4. Improve patient compliance
5. Improve oral absorption

The present study is to develop immediate release megesterol acetate tablets by using a novel technique mixed hydrotropy with different polymers by using different hydrotropic agents and super disintigrents at different ratios.

To fulfil the above scope the major objects of the investigations are as follows

1. To design megesterol acetate immediate release tablets.
2. To conduct preformulation studies of the API.
3. To prepare poorly soluble megesterol acetate tablets by using solid dispersion and mixed hydrotropy technique.
4. The primary object of this study was to enhance solubility of megesterol acetate.
5. To study the influence of polymer concentration on the megesterol acetate to optimise best polymer.
6. To optimise better technique.
7. To determine rate of dissolution.
8. To evaluate kinetic mechanisms of drug release.
9. To evaluate and prepare tablets as per pharmacopeia standards.

CHAPTER-1

INTRODUCTION

1.1.CANCER

A tumour is a swelling or mass resulting from abnormal growth of tissue. Cancer is likely to damage important or vital organs or tissue in any or all part of the body.

Cancer is a class of diseases characterized by out-of-control cell growth. There are over 100 different types of cancer, and each is classified by the type of cell that is initially affected

1.1.2. Types of cancer

1. **Leukaemia:** cancer of blood in which white blood cells shown an abnormal increase
2. **Carcinomas:** cancer of epithelial cells
3. **Sarcomas:** cancer of connective tissue
4. **Lymphomas:** cancer of lymphatic tissue
5. **Lipomas:** cancer of adipose tissue

1.1.3. Location for cancer

Cancer occurring in any part of body has unique characteristic

1. **Bile ducts:**

The bile ducts may become involved either with cancer developing within the ducts themselves or with cancer in adjacent structures. The earlier significant symptom in jaundice, which results from continuous obstruction to flow of bile.

2. **Breast:**

The breast is the common site of cancer in women lumps in the breast is caused by cancer. So the physician is dealing with early case of lump in the breast, has to differentiate between benign tumour and malignant one.

3. Bone:

The cancer of bone grows due to blood streams or from some adjacent organ or tissues. Bones cancer causes pain swelling and weakens the bone.

4. Esophagus:

Cancer of esophagus is also common it may occur in any part of organ from the throat on down, but mostly in the lower part. Due to cancer of esophagus there is difficulty in the swallowing.

5. Lung:

The cancer of lings is becoming more prominent in our country which causes maximum death in our country. The main reason for the lung cancer is cigarette without treatment the survival rate for the usual type of lung cancer is zero. In the total type of cancer 40% are infected by the lung cancer.

6. Ovary:

This is the most dreadful cancer amongst the women. The most of the women die due to cancer of ovary in our country. This can be treated by surgery

7. Pancreas:

The cancer of pancreas causes the pain in the upper part of the membrane. Cancer of pancreas also causes jaundice. The cancer is highly malignant cancer of pancreas is more common in men than women. This can be removed by surgery.

8. Stomach:

Cancer of stomach is also more common in men than women. Symptoms are indigestion, loss of appetite, loss of weight etc. Surgical removal without delay of all or part of the stomach is only proper treatment.

9. Thyroid:

This cancer causes the enlargement of thyroid gland, development of nodules in the gland. The removal of these nodules is very necessary for the treatment of this disease.

10. Tounge:

Cancer of tounge cause more death than any other cancer within the mouth. It results persistent inflammation.

1.2. BREAST CANCER

Breast tumours are usually caused by an overgrowth of the cells lining the breast ducts. They can be either benign or malignant. In a benign tumour, the cells grow abnormally and form a lump. But they don't spread to other parts of the body and so is not cancer. The most common type of benign breast tumour is called a fibro adenoma. This may need to be surgically removed to confirm the diagnosis. No other treatment is necessary. In a malignant tumour, the cancer cells have the ability to spread beyond the breast if they are left untreated. For example, if a malignant tumour in the breast isn't treated, it may grow into the muscles that lie under the breast. It can also grow into the skin covering the breast. Sometimes cells break away from the original (primary) cancer and spread to other organs in the body. They can spread through the bloodstream or lymphatic system. When these cells reach a new area they may go on dividing and form a new tumour. The new tumour is often called a secondary or metastasis. Breast cancer occurs when cells within the breast ducts and lobules become cancerous. If caught at an early stage, breast cancer can often be cured. If the cancer has spread to other areas of the body it can't usually be cured, but it can normally be effectively controlled for a long time.

1.2.1. Risk factors:

- **Age:**

  The risk of developing breast cancer increases with age. It's rare in women under 35. 8 out of 10 breast cancers (80%) occur in women aged 50 or over.

- **Previous cancer:**

1. Breast cancer, including ductal carcinoma in situ
2. Lobular carcinoma in situ
3. An over-production of slightly abnormal cells called atypical ductal hyperplasia
4. Radiotherapy to the chest to treat Hodgkin lymphoma at a young age

- **Hormonal factors:**

1. Taking combined hormone replacement therapy (HRT) containing oestrogen and progesterone over several years (if you're over 50)
2. Starting your periods early (under 12) or having a late menopause (after 50)
3. Taking the contraceptive pill (but the risk reduces if you stop taking it).

- **Certain lifestyle:**

  These include drinking more than two units of alcohol a day over many years, being overweight and smoking heavily.

- **Genetic factors:**

  Family history only 5–10% (1 in 20–1 in 10) of breast cancers is thought to be linked to an inherited breast cancer gene.

1.2.2. Symptoms

Symptoms of breast cancer can include:

• A lump in the breast

• A change in the size or shape of the breast

• Dimpling of the skin or thickening in the breast tissue

• A nipple that's turned in (inverted)

• A rash (like eczema) on the nipple

• Discharge from the nipple

• Swelling or a lump in the armpit.

1.2.3. Breast cancer diagnosed

- Mammogram
- Fine needle aspiration (FNA)
- Ultrasound and FNA of the lymph Nodes
- Biopsy of tissue
- Needle (core) biopsy
- CT (computerised tomography) scan
- MRI (magnetic resonance imaging) scan
- A breast ultrasound
- X- Rays ultrasound

1.3. **PROSTATE CANCER**

Prostate cancer is a form of cancer that develops in the prostate, a gland in the male reproductive system. Most prostate cancers are slow growing;[1] however, there are cases of aggressive prostate cancers.[2] The cancer cells may metastasize (spread) from the prostate to other parts of the body, particularly the bones and lymph nodes. Prostate cancer may cause pain, difficulty in urinating, problems during sexual intercourse, or erectile dysfunction. Other symptoms can potentially develop during later stages of the disease.

1.3.1. Symptoms

- These include frequent urination, nocturia (increased urination at night),
- Difficulty starting and maintaining a steady stream of urine,

- Hematuria (blood in the urine), and
- Dysuria (painful urination).

Prostate cancer is associated with urinary dysfunction as the prostate gland surrounds the prostatic urethra. Changes within the gland, therefore, directly affect urinary function. Advanced prostate cancer can spread to other parts of the body, possibly causing additional symptoms. The most common symptom is bone pain, often in the vertebrae (bones of the spine), pelvis, or ribs. Spread of cancer into other bones such as the femur is usually to the proximal part of the bone. Prostate cancer in the spine can also compress the spinal cord, causing leg weakness and urinary and fecal incontinence.

1.3.2. Risk factors

A complete understanding of the causes of prostate cancer remains elusive.[13] The primary risk factors are obesity, age and family history. Prostate cancer is very uncommon in men younger than 45, but becomes more common with advancing age

a. Genetic

Genetic background may contribute to prostate cancer risk, as suggested by associations with race, family, and specific gene variants.

b. Viral

In 2006, a previously unknown retrovirus, Xenotropic MuLV-related virus or XMRV, was associated with human prostate tumors, but subsequent reports on the virus were contradictory and the original 2006 finding was instead due to a previously undetected contamination.

c. Sexual factors

Several case-control studies have shown that having many lifetime sexual partners or starting sexual activity early in life substantially increases the risk of prostate cancer

1.3.3. Diagnosis

- Biopsy,
- Digital rectal examination (DRE).
- Cystoscopy
- Transrectal ultrasonography

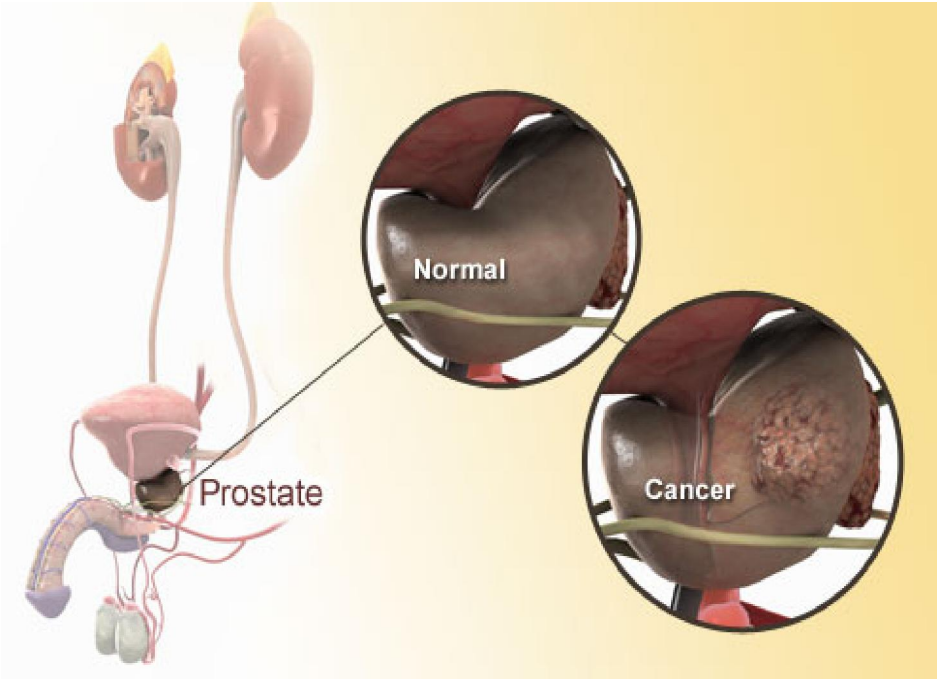


Fig no. 1. Diseased and normal prostate gland

1.4. Different types of chemotherapy drugs

Chemotherapy drugs can be divided into several groups based on factors such as how they work, their chemical structure, and their relationship to another drug. Because some drugs act in more than one way, they may belong to more than one group.

1.4.1. Alkylating agents

- Nitrogen mustards: such as mechlorethamine (nitrogen mustard), chlorambucil,

- Nitrosoureas: which include streptozocin, carmustine (BCNU), and lomustine
- Alkyl sulfonates: busulfan
- Triazines: dacarbazine (DTIC) and temozolomide (Temodar®)
- Ethylenimines: thiotepa and altretamine (hexamethylmelamine)

1.4.2. Antimetabolites

- 5-fluorouracil (5-FU), 6-mercaptopurine (6-MP) ,Capecitabine (Xeloda®), Cladribine, Floxuridine, Hydroxyurea, Methotrexate, Pentostatin, Thioguanine

1.4.3. Anti-tumour antibiotics

Anthracyclines

- Daunorubicin , Doxorubicin (Adriamycin®) , Epirubicin , Idarubicin

1.4.4. Other anti-tumor antibiotics

Topoisomerase inhibitors

Topoisomerase I inhibitors: Topotecan and irinotecan

Topoisomerase II inhibitors: Etoposide, teniposide, Mitoxantrone.

1.4.5. Mitotic inhibitors

- Taxanes: paclitaxel (Taxol®) and docetaxel (Taxotere®)
- Epothilones: ixabepilone (Ixempra®)
- Vinca alkaloids: vinblastine (Velban®), vincristine (Oncovin®), and vinorelbine
- Estramustine (Emcyt®)

1.4.6. Corticosteroids

Prednisone, methylprednisolone (Solumedrol®), and dexamethasone (Decadron®).

1.4.7. Other types of cancer drugs

a. Targeted therapies

Imatinib (Gleevec®), gefitinib (Iressa®), sunitinib (Sutent®) and bortezomib (Velcade®).

b. Differentiating agents

Retinoids, tretinoin (ATRA or Atralin®) and bexarotene (Targretin®), as well as arsenic trioxide (Arsenox®).

c. Hormone therapy

- The anti-estrogens: fulvestrant (Faslodex®), tamoxifen, and toremifene (Fareston®)
- Aromatase inhibitors: anastrozole (Arimidex®), exemestane (Aromasin®)
- Progestins:Megesterol acetate (Megace®)
- Estrogens
- Anti-androgens: bicalutamide (Casodex®), flutamide (Eulexin®)

d. Immunotherapy

- Monoclonal antibody therapy (passive immunotherapies), such as rituximab (Rituxan®) and alemtuzumab (Campath®)
- Non-specific immunotherapies and adjuvants (other substances or cells that boost the immune response), such as BCG, interleukin-2 (IL-2), and interferon-alfa
- Immunomodulating drugs, for instance, thalidomide and lenalidomide (Revlimid®)

1.5. SOLUBILITY:

Solubility is the property of a solid, liquid, or gaseous chemical substance called solute to dissolve in a solid, liquid, or gaseous solvent to form a homogeneous solution of the maximum quantity of solute in a certain quantity of solvent at a specified temperature and pressure

1.5.1. Process of Solubilisation:

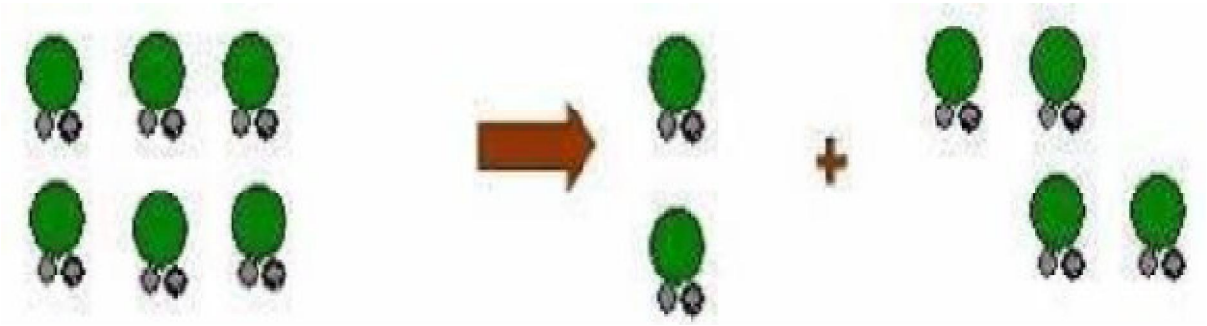
The process of solubilization contains three steps. First step involves the separation of the molecules of the solvent to provide space in the solvent for the solute, second step involves the breaking of intermolecular or inter-ionic bonds in the solute, and third & final step involves the interaction between the solvent and the solute molecule or ion.

TABLE 1: USP and BP solubility criteria

Descriptive term	Part of solvent required per part of solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very Slightly soluble	From 1000 to 10,000
Practically insoluble	10,000 and over

Step 1: Holes open in the solvent

Step2: Molecules of the solid breaks away from the bulk



Step 3:The freed solid molecule is integrated into the hole in the solvent

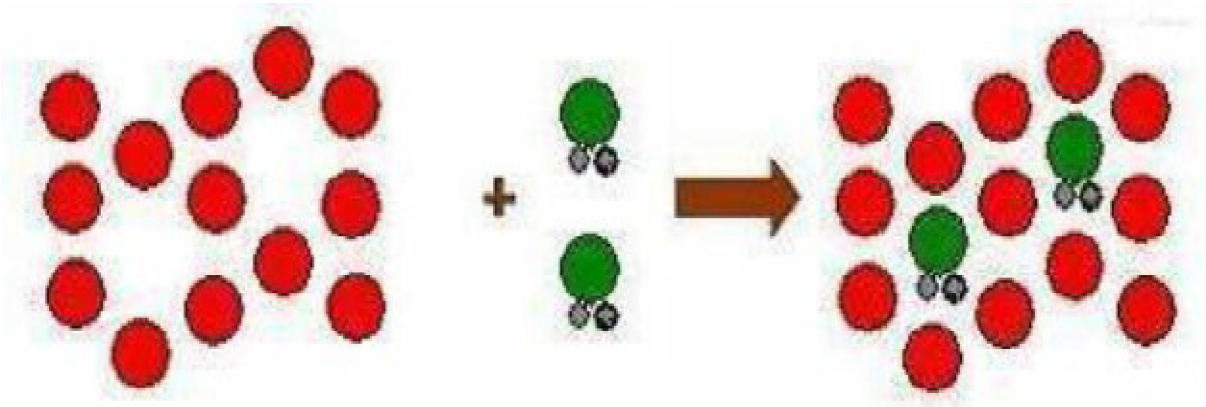


Fig no. 2 Solubilisation steps

1.5.2. BCS CLASSES:

According to the BCS (Biopharmaceutical classification system) all drugs have been divided into four classes:

- Class I— high soluble and high permeable,
- Class II—low soluble and high permeable,
- Class III—high soluble and low permeable and
- Class IV—low soluble and low permeable.

1.5.3. Importance of Solubility:

1. Especially for class II (low solubility and high permeability) substances according to the BCS, the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastro-intestinal fluids.

2. As for BCS class II drugs rate limiting step is drug release from the dosage form and solubility in the gastric fluid and not the absorption, so increasing the solubility in turn increases the bioavailability for BCS class II drugs.

3. The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastrointestinal fluids often cause insufficient bioavailability. so increasing the solubility in turn increases the bioavailability for them.

4. Solubility is one of the important parameters to achieve desired concentration of drug in systemic circulation for achieving required pharmacological response.

5. Poorly water soluble drugs often require high doses and have administration frequency in order to reach therapeutic plasma concentrations after oral administration.

6. Low aqueous solubility is the major problem encountered with formulation development of new chemical entities as well as generic development.

7. Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption.

8. Water is the solvent of choice for liquid pharmaceutical formulations.

9. Most of the drugs are either weakly acidic or weakly basic having poor aqueous solubility.

10. Poorly water soluble drugs having slow drug absorption leads to inadequate and variable bioavailability and gastrointestinal mucosal toxicity.

11. For orally administered drugs solubility is the most important one rate limiting parameter to achieve their desired concentration in systemic circulation for pharmacological response.

1.5.4. Enhancement of solubilization and bioavailability of poorly soluble drugs

Solubilization of poorly soluble drugs is a frequently encountered challenge in screening studies of new chemical entities as well as in formulation design and development .A number of methodologies can be adapted to improve solubilization of poor water soluble drug and further to improve its bioavailability. Orally administered drugs completely absorb only when they show fair solubility in gastric medium and such drugs shows good bioavailability. The techniques generally employed for solubilization of drug includes micronization, chemical modification, pH adjustment, solid dispersion, complexation, co?solvency, micellar solubilization, hydrotropy etc.

Actually, only solubilized drug molecules can be absorbed by the cellular membranes to subsequently reach the site of drug action . Any drug to be absorbed must be present in the form of an aqueous solution at the site of absorption . As Solubility & permeability is the deciding factor for the in-vivo absorption of the drug, these can be altered or modified by enhancement techniques like Poorly soluble compounds belongs to class II of BCS. These poorly water soluble drugs are allied with slow drug absorption leading to inadequate and variable bioavailability and gastrointestinal mucosal toxicity. Therefore, the improvement of drug solubility thereby its oral bio-availability remains one of most challenging aspects of drug development process especially for oral drug delivery system.

These in vivo and in vitro characteristics and the difficulties in achieving predictable and reproducible in vivo/in vitro correlations are often sufficiently difficult to develop formulation on many newly synthesized compounds due to solubility issues.

1.6. TECHNIQUES OF SOLUBILITY AND BIOAVAILABILITY ENHANCEMENT

There are various techniques available to improve the solubility of poorly soluble drugs.

Some of the approaches to improve the solubility are:

(1) **pH adjustment**

It is well documented that the influence of the changes in pH within the gastrointestinal tract upon the bioavailability of pharmaceuticals. The absorption of drug is largely dependent upon diffusion, which varies with pH of the individual regions within the gastrointestinal tract, the pKa of the drug and permeability, which are not only moderated by the surface area of the region in which it is released, but also the regional pH effects upon drug ionization. By applying a pH change, poorly water soluble drugs with parts of the molecule that can be protonated (base) or deprotonated (acid) may potentially be dissolved in water.

(2) Micro-emulsion

A micro emulsion is an optically clear pre-concentrate, isotropic, thermo dynamically stable transparent (or translucent) system, containing a mixture of oil, hydrophilic surfactant and hydrophilic solvent which dissolves a poorly water soluble drug. Upon contact with water, the formulations spontaneously disperse (or 'self emulsifies') to form a very clear emulsion of exceedingly small and uniform oil droplets containing the solubilized poorly soluble drug.

Micro-emulsions have been employed to increase the solubility of many drugs that are practically insoluble in water, along with incorporation of proteins for oral, parenteral, as well as percutaneous/transdermal use .These homogeneous systems, which can be prepared over a wide range of surfactant concentration and oil to water ratio, are all fluids of low viscosity. Surfactants, surfactant mixtures and co-surfactants in microemulsions play an important role

in improving the solubility of drugs formulated as micro-emulsions. An anhydrous system of micro-emulsions is that self microemulsifying drug delivery system (SMEDDS) or micro-emulsion pre-concentrate. It is composed of oil, surfactant and co-surfactant and has the ability to form o/w microemulsion when dispersed in aqueous phase under gentle agitation

(3) Self-emulsifying drug delivery systems

Self-emulsifying or self-micro emulsifying systems use the concept of in situ formation of emulsion in the gastrointestinal tract. The mixture of oil, surfactant, co-surfactant, one or more hydrophilic solvents and co-solvent forms a transparent isotropic solution that is known as the self-emulsifying drug delivery system (SEDDS) , in the absence of external phase (water) and forms fine o/w emulsions or micro-emulsions spontaneously upon dilution by the aqueous phase in the GIT and is used for improving lipophillic drug dissolution and absorption.

(4) Manipulation of solid state

From the stability and bioavailability aspects, the crystalline form of a drug is pharmaceutical importance. Polymorphism (existence of a drug substance in multiple crystalline forms) can cause variations in melting point, density, stability and drug solubility as these properties depend on the escaping tendency of the molecules from a particular crystalline structure. As a rule, for a drug that have the highest order of crystallinity is the most stable form, exists in multiple polymorphic forms, i.e. with the least amount of free energy, and, consequently, possesses the highest melting point and the least solubility. By controlling the crystallization process, amorphous or meta stable forms of drugs possessing high free energy can be forcibly created. They offer the advantage of higher solubility but suffer from stability issues unless stabilizers intended to inhibit crystal growth are incorporated in the formulation .

(5) Particle size reduction

The bioavailability of poorly soluble drugs is often intrinsically related to drug particle size. By reducing particle size, the increased surface area may improve the dissolution properties of the drug to allow a wider range of formulation approaches and delivery technologies . The larger surface area allows a greater interaction with the solvent which cause increase in solubility . Conventional methods of particle size reduction, such as comminution and spray drying, rely upon mechanical stress to disaggregate the active compound. Nowadays Particle size reduction can be achieved by micronization and nano-suspension.

- In Micronization of drugs is done by milling techniques using jet mill, rotor stator colloid mills etc.
- Nano-suspension is another technique which is sub-micron colloidal dispersion of pure particles of drug, which are stabilized by surfactants.

Nano-suspensions are produced by homogenization and wet milling process [43]. Re-crystallization of poorly soluble materials using liquid solvents and anti-solvents has also been employed successfully to reduce particle size.

(6) Super critical fluid (SCF) process

Another novel nano-sizing and solubilization technology whose application has increased in recent years is particle size reduction via supercritical fluid (SCF) processes. The number of applications and technologies involving supercritical fluids has also grown explosively. It has been known for more than a century that supercritical fluids (SCFs) can dissolve nonvolatile solvents, with the critical point of carbon dioxide, the most widely used supercritical fluid. Super critical fluids are fluids whose temperature and pressure are greater than its critical temperature (Tc) and critical pressure (Tp), allowing it to assume the properties of both a liquid and a gas. It is safe, environmentally friendly, and economical. The low operating conditions (temperature and pressure) make SCFs attractive for pharmaceutical research. At

nearcritical temperatures, SCFs are high compressible, allowing moderate changes in pressure to greatly alter the density and mass transport characteristics of a fluid that largely determine its solvent power . A SCF exists as a single phase above its critical temperature (Tc) and pressure (Pc). SCFs have properties useful to product processing because they are intermediate between those of pure liquid and gas (i.e., liquid-like density, gas-like compressibility and viscosity and higher diffusivity than liquids).At near-critical temperatures, SCFs are high compressible, allowing moderate changes in pressure to greatly alter the density and mass transport characteristics of a fluid that largely determine its solvent power .

(7) Inclusion complexes/complexation

Lipophillic drug-cyclodextrin complexes, commonly known as inclusion complexes, can be formed simply by adding the drug and excipients together, resulting in enhanced drug solubilization. Cyclodextrins (CD) are a group of structurally-related cyclic oligosaccharides that have a polar cavity and hydrophilic external surface. Inclusion complexes are formed by the insertion of the nonpolar molecule or the nonpolar region of one molecule (known as guest) into the cavity of another molecule or group of molecules (known as host). The most commonly used host molecules are cyclodextrins. Cyclodextrins consisting of 6, 7 and 8 D glucopyranosyl units connected to Q -1, 4 glycosidic linkages are known as Q, R, D, cyclodextrins, respectively. Derivatives of R-cyclodextrin with increased water solubility (e.g. hydroxypropyl-R-cyclodextrin HP-R-CD) are most commonly used in pharmaceutical formulation.

(8) Co-solvency

The solubility of a poorly water soluble drug can be increased frequently by the addition of a water miscible solvent in which the drug has good solubility known as cosolvents. Co solvents are mixtures of water and one or more water miscible solvents used to create a

solution with enhanced solubility for poorly soluble compounds. Historically, this is one of the most widely used techniques because it is simple to produce and evaluate Co-solvency has been utilized in different formulations including solids and liquids. Examples of solvents used in co-solvent mixtures are PEG 300, propylene glycol or ethanol. Various concentrations (5-40%) of the solid binary systems with polyethylene glycol 6000 were employed to increase solubility and dissolution. Co- Solvents can increase the solubility of poorly soluble compounds several thousand times compared to the aqueous solubility of the drug alone.

(9) Miceller solubilization

The use of surfactants to improve the dissolution performance of poorly soluble drug products has also been successfully employed. Surfactants can lower surface tension and improve the dissolution of lipophillic drugs in aqueous medium. They can also be used to stabilize drug suspensions. When the concentration of surfactants exceeds their critical micelle concentration (CMC, which is in the range of 0.05-0.10% for most surfactants), micelle formation occurs, entrapping the drugs within the micelles .This process is known as micellisation and generally results in enhanced solubility of poorly soluble drugs. Commonly used non-ionic surfactants include polysorbates, polyoxyethylated castor oil, polyoxyethylated glycerides, lauroyl macroglycerides and mono- and di-fatty acid esters of low molecular weight polyethylene glycols. Surfactants are also often used to stabilize micro-emulsions and suspensions into which drugs are dissolved.

(10) Hydrotrophy

Hydrotrophy is a solubilization process whereby addition of a large amount of second solute results in an increase in the aqueous solubility of another solute. Hydrotrophy designate the increase in solubility in water due to the presence of large amount of additives. The mechanism by which it improves solubility is more closely related to complexation involving a weak interaction between the hydrotropic agents like sodium benzoate, sodium acetate,

sodium alginate, urea and the poorly soluble drugs. Solute consists of alkali metal salts of various organic acids. Hydrotropic agents are ionic organic salts. Additives or salts that increase solubility in given solvent are said to "salt in" the solute and those salts that decrease solubility "salt out" the solute. Several salts with large anions or cations that are themselves very soluble in water result in "salting in" of non electrolytes called "hydrotropic salts" a phenomenon known as "hydrotropism". Hydrotropic solutions do not show colloidal properties and involve a weak interaction between the hydrotropic agent and solute.

The classification of hydrotropes on the basis of molecular structure is difficult, since a wide variety of compounds have been reported to exhibit hydrotropic behavior. Specific examples may include ethanol, aromatic alcohols like resorcinol, pyrogallol, catechol, aand bnaphthols and salicylates, alkaloids like caffeine and nicotine, ionic surfactants like diacids, SDS (sodium dodecyl sulphate) and dodecylated oxidibenzene.

(11) Solid Dispersions

In this technique, a poorly soluble drug is dispersed in a highly soluble solid hydrophilic matrix, which enhances the dissolution of the drug. Solid dispersion techniques can yield eutectic (non-molecular level mixing) or solid solution (molecular level mixing) products.

Eutectic dispersions are homogeneous dispersions of crystalline or amorphous drugs in crystalline or amorphous carriers. In the solid solution form, the drug could be partially or completely soluble in the dispersing matrix.

A solid dispersion of griseofulvin and polyethylene glycol 8000 (Gris- PEG®) is commercially available. Presence of the drug in microcrystalline state, improved wettability and formation of high free energy amorphous forms of the drug during solid dispersion formation contribute towards enhancement of drug solubilization.

Solid dispersions represent a useful pharmaceutical technique for increasing the dissolution, absorption and therapeutic efficacy of drugs in dosage forms. The most commonly used hydrophilic carriers for solid dispersions include polyvinylpyrrolidone, polyethylene glycols, Plasdone-S630, Tween-80, Docusate sodium, Myrj-52, Pluronic-F68 and Sodium Lauryl Sulphate used

Various techniques to prepare the solid dispersion of hydrophobic drugs to improve their aqueous solubility

1. Hot melt method (fusion method)

The physical mixture of a drug and a watersoluble carrier was heated directly until it melted. The melted mixture was then cooled and solidified rapidly in an ice bath under rigorous stirring. The final solid mass was crushed, pulverized, and sieved, which can be compressed into tablets with the help of tabletting agents. The melting point of a binary system is dependent upon its composition, i.e., the selection of the carrier and the weight fraction of the drug in the system.

2. Solvent Evaporation Method

The first to dissolve both the drug and the carrier in a common solvent and then evaporate the solvent under vacuum to produce a solid solution. This enabled them to produce a solid solution of the highly lipophillic R-carotene in the highly water soluble carrier polyvinylpyrrolidone. Many investigators studied solid dispersion of meloxicam15, naproxen and nimesulide using solvent evaporation technique.

3. Hot melt extrusion

Hot melt extrusion is essentially the same as the fusion method except that intense mixing of the components is induced by the extruder. Just like in the traditional fusion process, miscibility of drug and matrix can be a problem. High shear forces resulting in high local temperature in the extruder is a problem for heat sensitive materials.

(12) Nano-suspension

Nano-suspension technology has been developed as a promising candidate for efficient delivery of hydrophobic drugs. This technology is applied to poorly soluble drugs that are insoluble in both water and oils. The particle size distribution of the solid particles in nano-suspensions is usually less than one micron with an average particle size ranging between 200 and 600 nm. There are various methods for preparation of Nano-suspension includes Media Milling (Nanocrystals), High Pressure Homogenization in water (Dissocubes), High Pressure Homogenization in nonaqueous media (Nanopure) and combination of Precipitation and High-Pressure Homogenization (Nanoedege).

(13) Cryogenic techniques

Cryogenic techniques have been developed to creating nano-structured amorphous drug particles with high degree of porosity at very low temperature conditions so enhance the dissolution rate of drugs. Cryogenic inventions can be defined by the type of injection device (capillary, rotary, pneumatic and ultrasonic nozzle), location of nozzle (above or under the liquid level) and the composition of cryogenic liquid (hydro fluoro alkanes, N2, Ar, O2 and organic solvents). After cryogenic processing, dry powder can be obtained by various drying processes (spray freeze drying, atmospheric freeze drying, vacuum freeze drying and lyophilization).

(14) Nano-crystallization

The nanocrystallization is defined as a way of diminishing drug particles to the size range of 1-1000 nanometers. There are two distinct methods used for producing nanocrystals; 'bottom-up' and 'top-down' development. The top-down methods (i.e. Milling and High pressure homogenization) start milling down from macroscopic level, e.g. from a powder that is micron sized. In bottom-up methods (i.e. Precipitation and Cryo-vacuum method), nanoscale materials are chemically composed from atomic and molecular components.

1.7. IMMEDIATE RELEASE DRUG DELIVERY SYSTEM

Immediate release drug delivery system is also conventional type of drug delivery system and it is defined as - Immediate release tablets are designed to disintegrate and release their medicaments with no special rate controlling features such as special coatings and other techniques.

1.7.1. Advantages of immediate release drug delivery systems[2]

- Release the drug immediately.
- More flexibility for adjusting the dose.
- It can be prepared with minimum dose of drug.
- There is no dose dumping problem.
- Immediate release drug delivery systems used in both initial stage and final stage of disease.

Immediate release tablets (conventional tablets): The tablet is intended to be released rapidly after administration or the tablet is dissolved and administered as solution. It is the most common type and includes:

CHAPTER-2

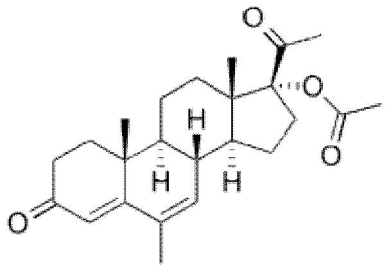
DRUG PROFILE

2.1. 1. MEGESTEROL ACETATE:

Generic name : Megace and Megace ES

Category : Antineoplastic Agents

Chemical structure :



Chemical and IUPAC name : (1S, 2R,10R,11S,14R,15S)-14-acetyl-14-hydroxy-2,15-dimethyltetracyclo[8.7.0.0^{2,7}.0^{11,15}]heptadeca6,8-dien-5-one.

Molecular formula : $C_{24}H_{32}O_4$

Molecular weight : 384.509 g/mol

Physical data:

Colour : white, crystalline solid

Odour : none.

Taste : bitter

Solubility : practically insoluble in water, soluble in acetone, sparingly soluble in alcohol.

Storage Conditions : Protected from light.

Melting point **:** about 217 °C.

Mechanism of action of Megesterol acetate:

The precise mechanism by which Megesterol acetate produces effects in anorexia and cachexia is unknown at the present time, but its progestin antitumour activity may involve suppression of luteinizing hormone by inhibition of pituitary function. Studies also suggest that the Megesterol's weight gain effect is related to its appetite-stimulant or metabolic effects rather than its glucocorticoid-like effects or the production of edema. It has also been suggested that Megesterol may alter metabolic pathyways via interferences with the production or action of mediators such as cachectin, a hormone that inhibits adipocyte lipogenic enzymes.

Pharmacodynamics of Megesterol Acetate

Megesterol Megesterol acetate significantly increases both appetite and bodyweight. In doses ranging from 160 to 1600 mg/day, Megesterol acetate shown to stimulate appetite, increase caloric intake, induce a sense of wellbeing, and produce weight gain. Weight gain occurs predominantly in the form of fat, which is of fat, which is potentially beneficial because the caloric stores in fatty tissue provide more kilocalories per gram than similar amounts of either protein or carbohydrate (i.e. 9.0 kcal vs 4.0 kcal and 4.0 kcal, respectively). Fat also helps stabilize core body temperatures and protects bony tissue; for example, the fat pads in the hips can help protect debilitated patients from hip fractures secondary to falls.

Pharmacokinetics of Megesterol Acetate

Megesterol acetate is absorbed rapidly from the gastrointestinal tract. However, studies in patients given the oral suspension demonstrate considerable variability in the rate and degree of

absorption; a factor that may be more significant in patients receiving the tablet formulation. In some patients, absorption is slower, with the more sustained plasma drug levels seen in a 1-compartment model. In others, absorption is rapid, with a 2-compartment-like elimination curve. Megesterol acetate is completely metabolized in the liver to free steroids and the metabolites are conjugated with glucuronic acid. Metabolites account for only 5–8% of the administered dose, which is considered negligible. The major route of drug elimination in humans is renal.

Indications and usage:

Megesterol acetate tablets are indicated for the palliative treatment of advanced carcinoma of the breast or endometrium (i.e., recurrent, inoperable, or metastatic disease). It should not be used in lieu of currently accepted procedures such as surgery, radiation, or chemotherapy.

Adverse reactions:

Weight Gain

Weight gain is a frequent side effect of Megesterol. This gain has been associated with increased appetite and is not necessarily associated with fluid retention.

Thromboembolic Phenomena

Thromboembolic phenomena including thrombophlebitis and pulmonary embolism (in some cases fatal) have been reported.

Other Adverse Reactions

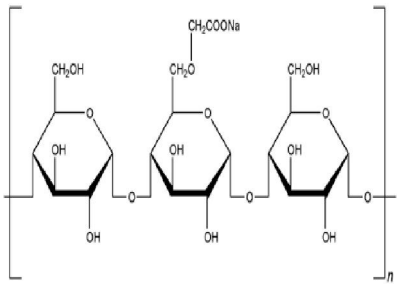
Heart failure, nausea and vomiting, edema, breakthrough menstrual bleeding, dyspnea, tumor flare (with or without hypercalcemia), hyperglycemia, glucose intolerance, alopecia, hypertension, carpal tunnel syndrome, mood changes, hot flashes, malaise, asthenia, lethargy, sweating and rash.

2.1.2. SODIUM STARCH GLYCOLATE

Synonyms: Carboxymethyl starch, sodium salt, carboxymethylamylum natricum.

Chemical Name and CAS Registry Number: Sodium carboxymethyl starch [9063-38-1].

Structural Formula:



Functional Category: Tablet and capsule disintegrant.

Description: Sodium starch glycolate is a white or almost white free-flowing very hygroscopic powder.

Solubility: Practically insoluble in methylene chloride. It gives a translucent suspension in water.

Stability and Storage Conditions: Tablets prepared with sodium starch glycolate have good storage properties. Sodium starch glycolate is stable although very hygroscopic, and should be stored in a well-closed container in order to protect it from wide variations of humidity and temperature, which may cause caking. The physical properties of sodium starch glycolate remain unchanged for up to 3 years if it is stored at moderate temperatures and humidity.

Incompatibilities: Sodium starch glycolate is incompatible with ascorbic acid.

Applications in Pharmaceutical Formulation or Technology:

- Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations.

- It is commonly used in tablets prepared by either direct-compression or wet-granulation processes. The usual concentration employed in a formulation is between 2% and 8%, with the optimum concentration about 4%, although in many cases 2% is sufficient.
- Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling.
- Although the effectiveness of many disintegrants is affected by the presence of hydrophobic excipients such as lubricants, the disintegrant efficiency of sodium starch glycolate is unimpaired. Increasing the tablet compression pressure also appears to have no effect on disintegration time.
- Sodium starch glycolate has also been investigated for use as a suspending vehicle.

2.1.3. MANNITOL

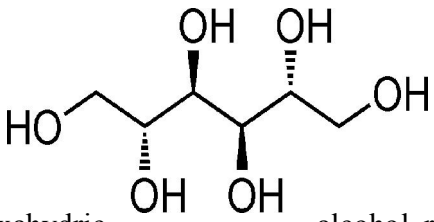
Synonyms: Cordycepic acid; 421; D- mannitol; manna sugar, mannite

Chemical name CAS Registry Number: D- mannitol. [69-65-8]

Empirical formula: C6H14O6.

Molecular weight: 182.17

Structural formula:



Description:

It is a hexahydric alcohol related to mannose and isomeric with sorbital Mannitol occurs as a white, odourless, crystalline powder or free flowing granules. It has a sweet taste approximately as sweet as glucose and half as sweet as sucrose and imparts a cooling sensation in mouth. Microscopically, it appears as orthorhombic needles when crystallized from alcohol.

Functional categories: Sweetening agent; tablet and capsule diluent; tonicity agent; vehicle (bulking agent) for lyophilized preparation.

Solubility: It is soluble in alkalis, in ethanol (95%) 1 in 83 in ether practically insoluble in glycerin 1 in 18, water 1 in 5.5.

Stability and storage: It is stable and should be stored in well closed container in a cool, dry place.

Incompatibilities: Not reported in dry state

Applications in Pharmaceutical Formulations or technology:

- Mannitol is widely used in pharmaceutical formulations and food products.
- In pharmaceutical preparations it is primarily used as a diluent (10–90% w/w) in tablet formulations, where it is of particular value since it is not hygroscopic and may thus be used with moisture-sensitive active ingredients.
- Mannitol may be used in direct-compression tablet applications for which the granular and spray-dried forms are available, or in wet granulations.
- Granulations containing mannitol have the advantage of being dried easily
- Specific tablet applications include antacid preparations, glyceryl trinitrate tablets, and vitamin preparations.
- Mannitol is commonly used as an excipient in the manufacture of chewable tablet formulations because of its negative heat of solution, sweetness, and 'mouthfeel'
- Mannitol has also been used to prevent thickening in aqueous antacid suspensions of aluminum hydroxide (<7% w/v). It has been suggested as a plasticizer in soft-gelatin capsules, as a component of sustained-release tablet formulations, and as a carrier in dry powder inhalers. It is also used as a diluent in rapidly.

2.1.4. CROSSPOVIDONE

Synonyms: Crospovidonum, crosslinked povidone, PVPP, Insoluble PVP Polyplasdone XL; Polyplasdone XL-10; polyvinylpolypyrrolidone.

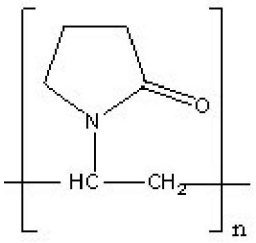
Chemical Name and CAS Registry Number:

1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

Empirical Formula and Molecular Weight

(C6H9NO) n >10, 00, 000

Structural Formula:



Description:

White, free flowing, compressible powder. A synthetic homopolymer of cross-linked N-vinyl-2-pyrrolidone.

Solubility:

Practically insoluble in water, acids, alkalis, and all organic solvents. Hygroscopic. Swells rapidly in water. Rapidly disperses in water, but does not gel even after prolonged exposure.

Functional Category: Super-disintegrant

Pharmacopeial Specifications

pH: pH (10% slurry): 5.0 – 8.0

Typical Properties

Acidity/alkalinity: pH= 5.0–8.0 for a 10% w/v aqueous solution

Applications in Pharmaceutical Formulation or Technology

- Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2–5% concentration in tablets prepared by direct compression or wet- and dry-granulation methods.
- Stabilizers for beer, vinegar, fruit and wine, prolonging the storage life.
- Disintegrants and fillers in pharmaceutical tablets and capsules.
- Detoxicants in detoxifiers or toxin absorbents.
- Stabilizers for moisture sensitive active ingredients (e. G. Vitamins, enzymes).
- Crospovidone can also be used as a solubility enhancer.
- With the technique of co-evaporation, crospovidone can be used to enhance the solubility of poorly soluble drugs.

2.1.5. TALC

Synonyms: Hydrous magnesium calcium silicate, powdered talc.

Chemical Name and CAS Registry Number: Talc [14807-96-6]

Empirical Formula and Molecular Weight: Talc is a purified, hydrated, magnesium silicate, approximating to the formula, Mg6 (Si2O5)4(OH) 4.

Functional Category: Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.

Description: Talc is a very fine, white to grayish-white, odorless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

Stability and Storage Conditions: Talc is a stable material and may be sterilized by heating at 1608C for not less than 1 hour. It may also be sterilized by exposure to ethylene oxide or gamma irradiation. Talc should be stored in a well-closed container in a cool, dry place.

Incompatibilities:

Incompatible with quaternary ammonium compounds

Applications in Pharmaceutical Formulation or Technology:

- Talc was once widely used in oral solid dosage formulations as a lubricant and diluent.
- It is widely used as a dissolution retardant in the development of controlled-release products.
- Talc is also used as a lubricant in tablet formulations, in a novel powder coating for extended-release pellets, and as an adsorbant.
- In topical preparations, talc is used as a dusting powder, although it should not be used to dust surgical gloves.

2.1.6. SODIUM ACETATE:

Synonyms:

Acetic acid, sodium salt; E262; natrii acetas trihydricus; sodium ethanoate.

Chemical Name and CAS Registry Number:

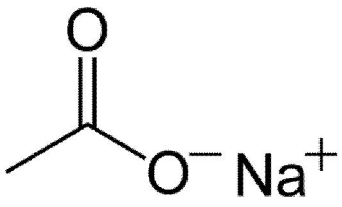
Sodium acetate anhydrous [127-09-3], Sodium acetate trihydrate [6131-90-4]

Empirical Formula and Molecular Weight

$C2H3NaO_2$ 82.0 (for anhydrous)

$C2H3NaO_23H2O$ 136.1 (for trihydrate)

Structural Formula



Description

Sodium acetate occurs as colorless, transparent crystals or a granular crystalline powder with a slight acetic acid odor.

Functional Category

Antimicrobial preservative, buffering agent, flavoring agent, stabilizing agent.

Solubility

Soluble 1 in 0.8 in water, 1 in 20 in ethanol (95%).

Applications in Pharmaceutical Formulation or Technology

- Sodium acetate is used as part of a buffer system when combined with acetic acid in various intramuscular, intravenous, topical, ophthalmic, nasal, oral, otic, and subcutaneous formulations. It may be used to reduce the bitterness of oral pharmaceuticals.
- It can be used to enhance the antimicrobial properties of formulations; it has been shown to inhibit the growth of S. aureus and E. coli, but not C. albicansin protein hydrolysate solutions.
- It is widely used in the food industry as a preservative.
- Sodium acetate has also been used therapeutically for the treatment of metabolic acidosis in premature infants and in hemodialysis solutions.

2.1.7. SODIUM BENZOATE:

Synonyms

Benzoic acid sodium salt; benzoate of soda; E211; natrii benzoas; natrium benzoicum; sobenate; sodii benzoas; sodium benzoic acid.

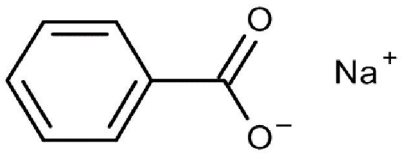
Chemical Name and CAS Registry Number

Sodium benzoate [532-32-1]

Empirical Formula and Molecular Weight

$C_7H_5NaO_2$ 144.1

Structural Formula



Description

Sodium benzoate occurs as a white granular or crystalline, slightly hygroscopic powder. It is odorless, or with faint odor of benzoin and has an unpleasant sweet and saline taste.

Functional Category

Antimicrobial preservative, tablet and capsule lubricant.

Solubility

Soluble 1 in 1.8 in water, 1 in 75 in ethanol (95%).

Applications in Pharmaceutical Formulation or Technology

- Sodium benzoate is used primarily as an antimicrobial preservative in cosmetics, foods, and pharmaceuticals.
- It is used in concentrations of 0.02–0.5% in oral medicines, 0.5% in parenteral products and 0.1–0.5% in cosmetics.
- Sodium benzoate is used in preference to benzoic acid in some circumstances, owing to its greater solubility.

- Sodium benzoate has also been used as a tablet lubricant(1) at 2–5% w/w concentrations. Solutions of sodium benzoate have also been administered, orally or intravenously, in order to determine liver function.

Stability and Storage Conditions

Aqueous solutions may be sterilized by autoclaving or filtration. The bulk material should be stored in a well-closed container, in a cool, dry place.

Incompatibilities

Incompatible with quaternary compounds, gelatin, ferric salts, calcium salts, and salts of heavy metals, including silver, lead, and mercury. Preservative activity may be reduced by interactions with kaolin or non ionic surfactants.

2.1.8. SODIUM CITRATE

Synonyms:

Citric acid trisodium salt; sodium citrate tertiary; trisodium citrate.

Chemical Name and CAS Registry Number:

Trisodium 2-hydroxypropane-1,2,3-tricarboxylate dehydrate [6132-04-3]

Empirical Formula and Molecular Weight:

C6H5Na3O7_2H2O 294.10

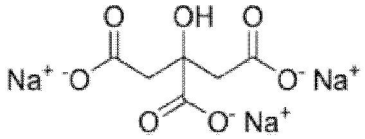
Functional Category:

Alkalizing agent; buffering agent; emulsifying agent; sequestering agent.

Description:

Sodium citrate dihydrate consists of odorless, colorless, monoclinic crystals, or a white crystalline powder with a cooling, saline taste. It is slightly deliquescent in moist air, and in warm dry air it is efflorescent.

Structural Formula:



Solubility:

Soluble 1 in 1.5 of water, 1 in 0.6 of boiling water, practically insoluble in ethanol (95%).

Applications in Pharmaceutical Formulation or Technology:

- Sodium citrate, as either the dihydrate or anhydrous material, is widely used in pharmaceutical formulations.
- It is used in food products, primarily to adjust the pH of solutions.
- It is also used as a sequestering agent.
- The anhydrous material is used in effervescent tablet formulations.
- Sodium citrate is additionally used as a blood anticoagulant either alone or in combination with other citrates such as disodium hydrogen citrate.
- Therapeutically, sodium citrate is used to relieve the painful irritation caused by cystitis, and also to treat dehydration and acidosis due to diarrhea.

2.1.9. MAGNESIUM STEARATE

Synonyms

Dibasic magnesium stearate; magnesium distearate; magnesia stearas; magnesium octadecanoate; magnesium salt; stearic acid, magnesium salt.

Chemical Name and CAS Registry Number

Octadecanoic acid magnesium salt [557-04-0]

Empirical Formula and Molecular Weight

C36H70MgO4 591.24

Structural Formula

[CH3 (CH2)16COO]2 Mg

Functional Category

Tablet and capsule lubricant.

Applications in Pharmaceutical Formulation or Technology

- Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations.
- It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams

Description

Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

2.2. POLYETHYLENE GLYCOL (PEG) 6000:

Synonyms

Polyglycol, Polyethylene oxide, Polyoxy ethylene, PEG 6000

Chemical Name and CAS Registry Number

a-Hydro-o-hydroxypoly(oxy-1,2-ethanediyl) [25322-68-3]

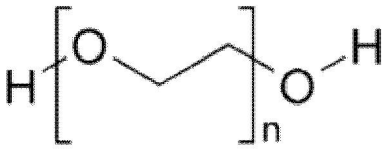
Empirical Formula and Molecular Weight

$H(OCH_2CH_2)nOH$ 6000

Functional Category

Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant.

Structural Formula



Description

The USP32–NF27 describes polyethylene glycol as being an addition polymer of ethylene oxide and water. Polyethylene glycol grades 200–600 are liquids; grades 1000 and above are solids at ambient temperatures. Solid grades (PEG>1000) are white or off-white in color, and range in consistency from pastes to waxy flakes. They have a faint, sweet odor. Grades of PEG 6000 and above are available as free flowing milled powders.

Solubility

Solid polyethylene glycols are soluble in acetone, dichloromethane, ethanol (95%), and methanol; they are slightly soluble in aliphatic hydrocarbons and ether, but insoluble in fats, fixed oils, and mineral oil.

Applications in Pharmaceutical Formulation or Technology

- Polyethylene glycols (PEGs) are widely used in a variety of pharmaceutical formulations, including parenteral, topical, ophthalmic, oral, and rectal preparations.
- Polyethylene glycol has been used experimentally in biodegradable polymeric matrices used in controlled-release systems.
- Polyethylene glycol 6000 is listed as an ophthalmic demulcent active ingredient.

- Polyethylene glycols are stable, hydrophilic substances that are essentially nonirritant to the skin.
- In solid-dosage formulations, higher-molecular-weight polyethylene glycols can enhance the effectiveness of tablet binders and impart plasticity to granules.
- Polyethylene glycols can also be used to enhance the aqueous solubility or dissolution characteristics of poorly soluble com pounds by making solid dispersions with an appropriate polyethylene glycol.
- Polyethylene glycol grades with molecular weights of 6000 and above can be used as lubricants, particularly for soluble tablets.

2.2.1. MICRCRYSTALLINE CELLULOSE (AVICEL pH 102)

Synonyms

Avicel PH; Cellets; Celex; cellulose gel; hellulosum microcristall num; Celphere; Ceolus KG; crystalline cellulose.

Chemical Name and CAS Registry Number

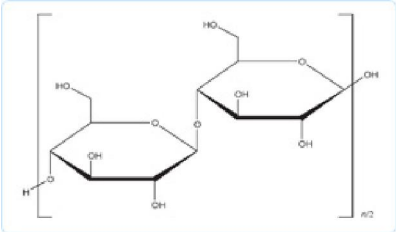
Cellulose [9004-34-6]

Empirical Formula and Molecular Weight

$(C_6H_{10}O_5)_n \approx 36\,000$

where $n \approx 220$.

Structural Formula



Functional Category

Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant

Description

Microcrystalline cellulose is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

Applications in Pharmaceutical Formulation or Technology

- Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes.
- Enhance drug dissolution by speeding tablet disintegration.
- Improves flow, better compressibility, Accommodation of moisture-sensitive actives.
- Microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting.

UREA

Synonyms

Biopure 100; Germall 115; imidazolidinyl urea; 1,10- methylenebis{3-[3-(hydroxymethyl)-2,5-dioxo-4-imidazolidinyl] urea}.

Chemical Name and CAS Registry Number

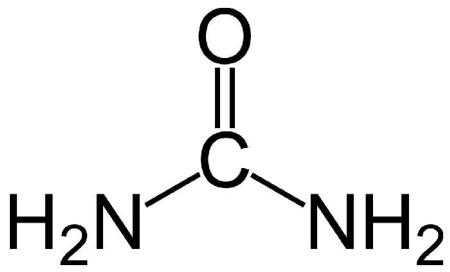
N, N00-Methylenebis {N0-[3-(hydroxymethyl)-2, 5-dioxo-4-imidazolidinyl] urea} [39236-46-9]

Empirical Formula and Molecular Weight

C11H16N8O8 388.29 (for anhydrous)

C11H16N8O8.H2O 406.33 (for monohydrate)

Structural Formula



Functional Category

Antimicrobial preservative.

Description

Imidurea is a white, free-flowing odorless powder.

Solubility

Soluble in water and in glycerol, but insoluble in almost all organic solvents.

Incompatibilities

Imidurea is incompatible with strong oxidants. It is compatible with other preservatives including sorbic acid and quaternary ammonium compounds.

Applications in Pharmaceutical Formulation or Technology

- Imidurea is a broad-spectrum antimicrobial preservative used in cosmetics and topical pharmaceutical formulations; typical concentrations used are 0.03–0.5% w/w.
- It is effective between pH 3–9 and is reported to have synergistic effects when used with parabens.
- It is used as hydrotropic agent.

CHAPTER -3

LITERATURE REVIEW

3.1. Shinde S.S1, Patil S.S. 1, Mevekari F.I. 1, Satpute A.S. *An approach for solubility enhancement: solid dispersion.* Objective of this work is to improve the solubility and dissolution rate of poorly water soluble Aceclofenac by solid dispersion method followed by solvent evaporation method. And to compare effectiveness of hydrophilic polymer PVP-k30, HPMC E-5, using porous carrier Aerosil 200. , resultant complexes were evaluated for drug content, infrared spectroscopy, and XRD and dissolution study. International Journal of Advances in Pharmaceutical Sciences 1 (2010) 299-308.

3.2. Biresh Sarkar, Devananda Jain, Shailendra Singh Solanki. *Improvement of Solubility of Flavonoids by Using Different Solubilization Techniques.* Quercetin one of the most common flavonoids reported to possess numerous pharmacological activities and shows poor aqueous solubility. In order to improve solubility and dissolution rate of quercetin different solubilisation techniques like; hydrotropic solubilization, mixed hydrotropy and hydrotropic solid dispersions were used. The objective was also aimed to explore the application of different hydrotropic agents at their optimum concentration; thus decreases the chances of their own toxicity. Result concluded that the toxic level of hydrotropic agents was decreased because their minimum concentrations were found to be sufficient to produced desired results.

3.3. Kapadiya Nidhi, Singhvi Indrajeet, Mehta Khushboo. *Hydrotropy: A Promising tool for solubility enhancement: A Review.* The study on solubility yields information about the structure and intermolecular forces of drugs. Hydrotropy is one of the solubility enhancement techniques which enhance solubility to many folds with use of hydrotropes like sodium benzoate, sodium citrate, urea, niacinamide etc. and have many advantages like; it does not require chemical modification of hydrophobic drugs, use of organic solvents, or

preparation of emulsion system etc. International Journal of Drug Development & Research April-June 2011, Vol. 3, Issue 2.

3.4. K.P.R. Chowdary and Veeraiah Enturi. *Enhancement of Dissolution Rate and Formulation Development of Efavirenz Tablets Employing Starch Citrate-A New Modified Starch.* Starch as a carrier in solid dispersions for enhancing the dissolution rate of efavirenz. The feasibility of formulating solid dispersions of efavirenz in starch citrate into compressed tablets with enhanced dissolution rate was also investigated. Starch citrate was prepared by reacting starch with citric acid at elevated temperatures. It was insoluble in water and has good swelling (1500%) property without pasting or gelling when heated in water. Solid dispersions of efavirenz in starch citrate were prepared by solvent evaporation method employing various weight ratios of drug: starch citrate such as 2:1(SD-1), 1:1(SD-2), 1:2(SD-3), 1:3(SD-4) and 1:9(SD-5) and were evaluated for dissolution rate and efficiency. All the solid dispersions prepared gave rapid and higher dissolution of efavirenz when compared to pure drug. Journal of Applied Pharmaceutical Science 01 (05); 2011: 119-123.

3.5. R. C. Doijad, A. B. Pathan, S. S.Gaikwad, S. S. Baraskar N. B. Pawar, V. D. Maske. *Liquisolid: A Novel Technique for Dissolution Enhancement of Poorly Soluble Drugs.* The poor dissolution characteristic of water insoluble drugs is a major challenge for formulation scientists. According to the new formulation method of liquisolid compacts, liquid medications such as solutions or suspensions of water insoluble drugs in suitable nonvolatile liquid vehicles can be converted into acceptably flowing and compressible powders by blending with selected powder excipients. In this case, even though the drug is in a solid dosage form, it is held within the powder substrate in solution or, in a solubilized, almost molecularly dispersed state, which contributes to the enhanced drug dissolution and release properties. Current Pharma Research., Vol. **3**(1), 2012, 735-749.

3.6. Divya Theja, Vishnuvardhan Rao T , Jamuna P and Sabitha Reddy P. *An approach to increase solubility of Rifampicin by Solid dispersion technique.* Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. The purpose of this work was to describe the enhance solubility of rifampicin by using solid dispersion technique and Physical mixture with PEG6000. Here drug and carrier ratio 1:1, 1:2, 1:3 and 1:10 respectively. The prepared samples were evaluated by SEM, Drug content, *In-vitro* studies, Wettability and Solubility, IR studies, Angle of repose. *In-vitro* drug release showed fast and complete release over a period of 2hrs in pH7.4 release profile of solid dispersion (SD 10) were compared with pure drug and physical mixture. IJPSR, 2012; Vol. 3(6): 1800-1805.

3.7. S.Vidyadhara, J.Ramesh Babu, RLC.Sasidhar, A.Ramu, S.Siva Prasad and M.Tejasree. *Formulation and evaluation of Glimepiride solid dispertions and their tablet formulation for enhanced bioavailability.*Solid dispersions of Glimepiride with sodium starch glycolate (SSG) were prepared and further compressed as tablets by using diluents such as lactose, dicalcium phosphate and microcrystalline cellulose. The solid dispersions of Glimepiride with SSG at different ratios were prepared by physical mixing, solvent evaporation and kneading methods. The rapid release of poorly soluble Glimepiride from solid dispersions was influenced by the proportion of polymer and the method employed for its preparation. Among the three methods employed solvent evaporation and kneading methods were found to be suitable for improving the dissolution rate of Glimepiride. All the tablet preparations containing diluents were found to release the drug in the order of DCP> MCC > Lactose. PHARMANEST - An International Journal of Advances In Pharmaceutical Sciences Vol. 2 (1) January - February 2011.

3.8. Ganesh Chaulang*, Kundan Patil, Dhananjay Ghodke, Shagufta Khan and Pramod Yeole. *Preparation and Characterization of Solid Dispersion Tablet of Furosemide with Crospovidone.* This article investigates enhancement of the dissolution profile of furosemide using solid dispersion (SD) with crospovidone (CPV) by using kneading technique. 1:1 (w/w) and 1:2 (w/w) solid dispersions were prepared by kneading method using solvent water and ethanol in 1:1 ratio. Dissolution studies using the USP paddle method were performed for solid dispersions of furosemide at 37 ± 0.5oC and 50 rpm in simulated gastric fluid (SGF) of pH 1.2. Fourier transformer infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC), and x-ray diffractometry (XRD) were performed to identify the physicochemical interaction between drug and carrier, hence its effect on dissolution. Tablets were formulated containing solid dispersion products and compared with commercial products. Tablets containing solid dispersion exhibited better dissolution profile than commercial tablets. Research J. Pharm. and Tech. 1(4): Oct.-Dec. 2008.

3.9. Gaver RC, Pittman KA, Reilly CM, Goodson PJ, Breault GO, Fenzl E. *Evaluation of two new Megesterol acetate tablet formulations in humans.* The bioequivalence of two new investigational 160 mg tablets, one containing the regular form and the other a micronized form of Megesterol acetate, was determined relative to a commercially available 40 mg tablet (Megace). The tablets were administered to 24 male subjects in a three-way cross-over study, balanced for sequence, with a week between administrations. The 40 mg tablets were administered q.i.d. at 08.00, 12.00, 18.00 and 22.00 h, while the 160 mg tablets were administered once at 08.00 h. Plasma samples were collected at appropriate times out to 96 h after administration and were analysed for Megesterol acetate with a validated high performance liquid chromatographic procedure. Based on the times to maximum plasma concentrations (2.5 to 2.8 h), the absorption rate constant was the same for each of the tablets. Relative to the 40 mg q.i.d. dose, the 160 mg regular and the 160 mg micronized tablets had

mean relative bioavailabilities of 97 per cent and 118 per cent, respectively. Biopharmaceutics and drug disposition, 1986 Jan-Feb; 7(1):35-46.

3.10. Hong SW, Lee BS, Park SJ, Jeon HR, Moon KY, Kang MH, Park SH, Choi SU, Song WH, Lee J, Choi YW. *Solid dispersion formulations of Megesterol acetate with copovidone for enhanced dissolution and oral bioavailability.* In order to enhance the dissolution profile and oral bioavailability of Megesterol acetate (MA), solid dispersions of MA (MASDs) were formulated with copovidone and crystal sugar as a hydrophilic polymeric carrier and an inert core bead, respectively. Solvent evaporation method and fluidized bed coating technique were employed. MASDs were categorized as crystalline solid dispersion by the characterization of differential scanning calorimetry and X-ray diffraction. Dissolution of MASD was gradually increased up to 15 min, after which it reached a plateau. For the initial period, dissolution rates were in the decreasing order of MASD (1:2) ≥ MASD (1:1) > MASD (1:3) > MASD (1:5) > MASD (1:0.5) > MA powder. In the comparative pharmacokinetic study with Megace OS, a reference drug product, MASD (1:1) showed improved bioavailability of over 220% with 2-fold higher C(max) and 30% faster T(max). We conclude that MASD (1:1) is a good candidate for the development of oral solid dosage forms. Archives of pharmaceutical research, 2011 Jan; 34(1):127-35.

3.11. Yellela S.R. Krishnaiah. *Pharmaceutical Technologies for Enhancing Oral Bioavailability of Poorly Soluble Drugs,* The oral bioavailability of BCS class II drugs with poor solubility and reasonable permeability is limited by drug dissolution step from drug products. The present reviews describes the main technologies such as micronization, crystal engineering, nanosizing, solid dispersion, cyclodextrins and other colloidal drug delivery systems with few relevant research reports. Journal of Bioequivalence & Bioavailability, Volume 2(2): 028-036 (2010).

3.12. B. Agaiah Goudb, J. Rajub and D. Rambhaua: IJPBS 2012, *Formulation and Evaluation of Megesterol Proniosomal Systems;* Over 40% of old and new drug molecules are implicated with poor oral bioavailability due to poor drug solubility in aqueous environment of gastro-intestinal lumen. Megesterol acetate, a synthetic derivative of the naturally occurring steroid hormone used to manage various disorders that affect women. Megesterol does not appear to be well absorbed from the gut. This may be related to its relative insolubility (2μg/ml) micronized formulations are more completely absorbed than are non micronized preparations. Liposomal drug products have shown improved oral bioavailability.

3.13. Robert A. Femia1 and Richert E. Goyette: Bio drugs 2005, *The Science of Megesterol Acetate Delivery Potential to Improve Outcomes in Cachexia*; Anorexia is considered a key component of the anorexia-Cachexia syndrome. Progestogens, particularly Megesterol acetate,

are commonly used to treat anorexia-Cachexia. The mechanism of action of Megesterol is believed to involve stimulation of appetite by both direct and indirect pathways and antagonism of the metabolic effects of the principal catabolic cytokines. Because the bioavailability of Megesterol acetate directly affects its efficacy and safety, the formulation was refined to enhance its pharmacokinetics.

3.14. Purwa Jain, Achhrish Goel, Shweta Sharma, Meghal Parmar: *Solubility Enhancement Techniques with Special Emphasis on Hydrotrophy;* Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. Drug efficacy can be severely limited by poor aqueous solubility and some drugs also show side effects due to their poor solubility. There are many techniques which are used to enhance the aqueous solubility. The ability to increase

aqueous solubility can thus be a valuable aid to increasing efficiency and/or reducing side effects for certain drugs. International Journal of Pharma Professional's Research 2010.

3.15. Soon Wook Hong, Bong Sang Lee1, Su Jun Park: *Solid Dispersion Formulations of Megesterol Acetate with Copovidone for Enhanced Dissolution and Oral Bioavailability:* In order to enhance the dissolution profile and oral bioavailability of Megesterol acetate (MA), solid dispersions of MA (MASDs) were formulated with Copovidone and crystal sugar as a hydrophilic polymeric carrier and an inert core bead, respectively. Solvent evaporation method and fluidized bed coating technique were employed. MASDs were categorized as crystalline solid dispersion by the characterization of differential scanning calorimetry and X-ray diffraction. Arch Pharm Res 2011.

3.16. Bhawana Kapoor, Ramandeep Kaur, Sukhdeep Kour: *Solid Dispersion: An Evolutionary Approach for Solubility Enhancement of Poorly Water Soluble Drugs.* Although the oral route of administration is the most common and preferred method of delivery due to convenience and ease of ingestion for many drugs it can be a tricky and inefficient mode of delivery for water-insoluble drugs with high permeability or Class II drugs in FDA's Biopharmaceutical Classification System (BCS). Such drugs typically exhibit dissolution rate limited absorption resulting in poor bioavailability when delivering via the oral route. Solid dispersion is a competent approach to deal with drugs that suffer from dissolution-limited absorption. This strategy has proven to improve the bioavailability by dispersing the hydrophobic drug as very fine particles within hydrophilic matrix that results in increased solubility with increased surface area available for dissolution. Int J Recent Adv Pharm Res, 2012.

3.17. Wiktoria Leśniak, Małgorzata Bała: *Effects of Megesterol acetate in patients with cancer anorexia-Cachexia syndrome – a systematic review and meta-analysis;* Megesterol acetate (MA) is a synthetic hormone (progestogen) used for the therapy of

hormone-dependent cancer, mainly endometrial cancer and less commonly breast cancer. This drug is also used for symptom relief in anorexia-cachexia syndrome (ACS) patients.1 This syndrome that occurs among other things in the advanced stage of cancer or in association with HIV infection, is characterized by weight and appetite loss, decline in muscle and adipose tissue mass, worsening of the performance status and decrease in the quality of life level (well-being). Pol Arch Med Wewn 2008.

3.18. H B Muss, L D Case, R L Capizzi, M R Cooper, J Cruz: *High- versus standard-dose Megesterol acetate in women with advanced breast cancer: a phase III trial of the Piedmont Oncology Association;* One hundred seventy-two patients with advanced breast cancer were randomized to receive oral standard-dose Megesterol acetate (MA), 160 mg/d or high-dose MA, 800 mg/d. All but two patients had one prior trial of tamoxifen therapy for either metastatic disease (74%) or as adjuvant treatment (26%). Pre-treatment characteristics were similar for both arms. High-dose MA resulted in a superior complete plus partial response rate (27% v 10%, P = .005), time to treatment failure (median, 8.0 v 3.2 months, P = .019), and survival (median, 22.4 v 16.5 months, P = .04) when compared with standard-dose therapy. These differences remained significant after adjustment for other covariates. American Society of Clinical Oncology 1990.

3.19. Robert A. Femia and Richert E. Goyet. *The Science of Megesterol Acetate Delivery. Potential to Improve Outcomes in Cachexiate.* Cachexia, usually defined as the loss of >5% of an individual's baseline bodyweight over 2–6 months, occurs with a number of diseases that includes not only AIDS and advanced cancer but also chronic heart failure, rheumatoid arthritis, chronic obstructive pulmonary disease, Crohn disease, and renal failure. Progestogens, particularly Megesterol acetate, are commonly used to treat anorexia-cachexia. The mechanism of action of Megesterol is believed to involve stimulation of appetite by both

direct and indirect pathways and antagonism of the metabolic effects of the principal catabolic cytokines. Because the bioavailability of Megesterol acetate directly affects its efficacy and safety, the formulation was refined to enhance its pharmacokinetics. Such efforts yielded Megesterol acetate in a tablet form, followed by a concentrated oral suspension form, and an oral suspension form developed using nanocrystal technology. Nanocrystal technology was designed specifically to optimize drug delivery and enhance the bioavailability of drugs that have poor solubility in water. Biodrugs 2005; 19 (3): 179-187.

CHAPTER 4

EXPERIMENTAL WORK

4.1: Materials used in the present research work.

Table No: 2 List of Materials

S.No	Name of the product	Name of the supplier
1	Megesterol acetate	Natco Pharma Pvt,Ltd.Hyderabad
2	PEG 6000	Finar chemicals limited,Ahmedabed
3	Sodium starch glycolate	Finar chemicals limited,Ahmedabed
4	Avicel pH 102	Natco Pharma Pvt,Ltd.Hyderabad
5	CrosspovidoneXL10	Natco Pharma Pvt,Ltd.Hyderabad
6	Mannitol	Finar chemicals limited,Ahmedabed
7	Urea	Finar chemicals limited,Ahmedabed
8	Sodium benzoate	Finar chemicals limited,Ahmedabed
9	Sodium acetate	Finar chemicals limited,Ahmedabed
10	Sodium citrate	Finar chemicals limited,Ahmedabed
11	Acetonitrile	Finar chemicals limited,Ahmedabed
12	Talc	Reidel (India) Chemicals, Hapur
13	Magnesium stearate	S.D.Fine-chem limited, Mumbai

4.2 Table 3: List of Equipments and Instruments used

S.No.	EQUIPMENTS	SOURCE
1	U.V/Visible spectrophotometer	Elico SL 159
2	Electronic Balance	Sartorius, German.
3	Rotary tablet compression machine	Cadmach, Ahmadabad.
4	Disintegration test apparatus	Electro Lab (ED-2L) Kshitij
5	pH Meter (pH 510)	Systronic, µ p^H system 365
6	USP Dissolution test apparatus XXIII	VEGO Disso 2000, Navi, Mumbai
7	Friabilator	Cintex,Mumbai
8	Hot Air Oven(temperature controlled µp Based	Servewell Instrument Pvt, Ltd, India.
9	Melting point apparatuses	Cintex , Mumbai
10	Stability Chamber	Labtop InstrumentPvt, Ltd, Bangalore.
11	Micro pippette's(100-1000µl)	Brand, German.
12	Hardness Tester	Monsanto, Mumbai.
13	Tap Density Apparatus	Campbell electronics, Mumbai.
14	FTIR	Jasco FTIR 6100 type-A, Japan.

4.3PREFORMULATION STUDIES:

Preformulation studies are the first step in the rational development of dosage form of a drug substance. Preformulation can be defined as investigation of physical and chemical properties of drug substance alone and when combined with excipients.

4.3.1Organoleptic characteristics:

The colour, odour, and taste of the drug were characterized and recorded using descriptive terminology.

Table 4: Organoleptic properties

Colour	Odour	Taste
Off white	Pungent	Acidic
Cream white	Sulfurous	Bitter
Tan	Fruity	Bland
Shiny	Aromatic	Intense
	Odorless	Sweet
		Tasteless

4.3.2Melting point depression

A characteristic of a pure substance is defined by its melting point or melting range. If not pure, the substance will exhibit a change in melting point. This phenomenon is commonly used to determine the purity of a drug substance and sometimes compatibility of various substances. It is Determined by Capillary method is using Melting point apparatus.

4.3.3SOLUBILITY DETREMINATION:

Solubility of Megesterol acetate was determined in ethanol, water and acetone. Solubility studies were performed by taking excess amount of Megesterol acetate in different beakers containing solvent. The mixtures were shaken for 24 hrs at regular intervals. The solutions were then filtered by using Whatmann's filter paper. The filtered solutions are analyzed spectrophotometrically.

Table 5: Solubility chart

Descriptive term	Approximate volume
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble	More than 10,000

4.3.4 MICROMERITIC PROPERTIES:

4.3.4.1 PARTICLE SHAPE & PARTICLE SIZE:

Bulk flow, formulation homogeneity, and surface-area controlled processes such as dissolution are directly affected by size, shape and surface morphology of the drug particles.

Fig 9: Particle shape

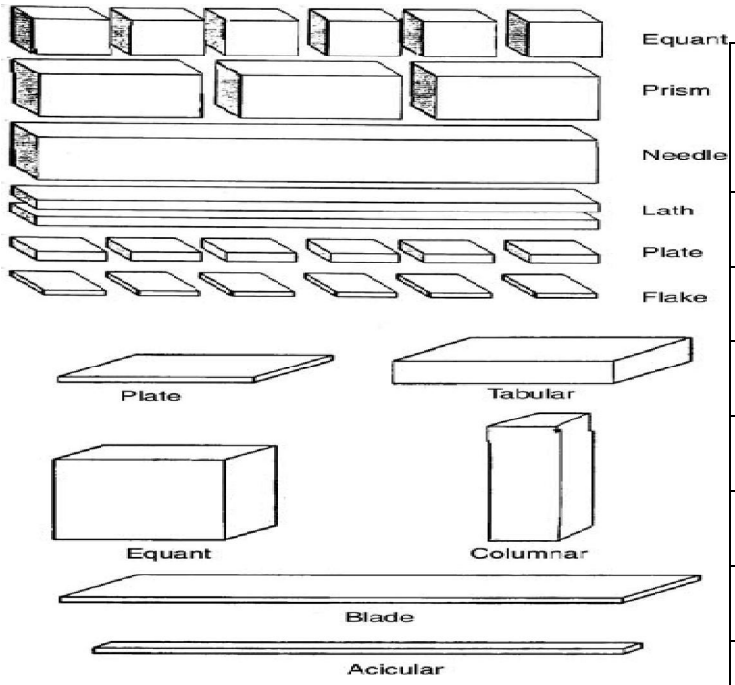


Table: 6 Particle size range

TECHNIQUE	SIZE RANGE
Microscopic	1 – 100
Sieve	> 50
Sedimentation	> 1
Elutriation	1 – 50
Centrifugal	< 50
Permeability	> 1
Light scattering	0.5 – 50

4.3.4.2 MICROSCOPY:

Optical microscopy is generally used as the first tool to see and measure sizes of particles ranging in size from 0.2 microns to 100 microns.

4.3.4.3 PARTITION COEFFICIENT (PO/W):

Partition coefficient (oil/water) is a measure of a drug's lipophilicity and an indication of its ability to cross cell membranes. It is defined as the ratio of un-ionized drug distributed between the organic and aqueous phases at equilibrium. The partition coefficient is commonly determined using an oil phase of octanol or chloroform and water.

Po/w = (Coil/Water) equilibrium

P value >1 –lipophilic drug, P value <1-hydrophilic drug

4.3.4.4 BULK DENSITY (D_b):

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder (passed through standard sieve # 20) into a measuring cylinder and initial weight was noted. This initial volume was called the bulk volume. It is expressed in gm/ml and is given by

$$D_b = M/V_b$$

M is the mass of powder

V_b is the bulk volume of the powder.

4.3.4.5 TAPPED DENSITY (D_t):

It is the ratio of total mass of the powder to the tapped volume of the powder. Volume was measured by tapping the powder for 750 times and the tapped volume was noted if the difference between these two volumes is less than 2%. If it is more than 2%, tapping is continued for 1250 times and tapped volume was noted. Tapping was continued until the difference between successive volumes is less than 2% (in a bulk density apparatus). It is expressed in gm/ml and is given by

$$D_t = M/V_t$$

M is the mass of powder

V_b is the tapped volume of the powder.

4.3.4.6 ANGLE OF REPOSE (Θ):

The friction forces in a loose powder can be measured by the angle of repose (**θ**). It is an indicative of the flow properties of the powder. It is defined as maximum angle possible between the surface of the pile of powder and the horizontal plane.

Tan (θ) = h/r	Where, θ is the angle of repose h is the height in cm & r is the radius in cm

The powder mixture was allowed to flow through the funnel fixed to a stand at define height (h). The angle of repose was then calculated by measuring the height and radius of the heap of powder formed.

Table 7 Angle of Repose as an Indication of Powder Flow Properties

Sr.No.	Angle of Repose (θ)	Type of Flow
1	<20	Excellent
2	20 – 30	Good
3	30 – 34	Passable
4	> 34	Very Poor

4.3.4.7 CARR'S INDEX (OR) % COMPRESSIBILITY: It indicates powder flow properties. It is expressed in percentage and is given by

$$I = \frac{D_t - D_b}{D_t} \times 100$$

Where, D_t is the tapped density and D_b is the bulk density of the powder.

Table 8: Relationship between % compressibility and flow ability

% Compressibility	Flow ability
5 -12	Excellent
12 – 16	Good
18 – 21	Fair Passable
23 – 35	Poor
33 – 38	Very Poor
< 40	Very Very Poor

4.3.4.8 HAUSNER'S RATIO: Hausner's ratio is an indirect index of ease of powder flow. It was calculated by the following formula.

Hausner's ratio= Dt/Db

Dt is tapped density

Db is bulk density

Table 9: Hausner's ratio

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Flow Characteristics	Hausner's Ratio
Excellent -no arching, Flow aid not needed	1.00-1.11
Good-aid not needed will not arch	1.12-1.18
Fair-Vibration may be needed	1.19-1.25
Passable-borderline, material may hang up	1.26-1.34
Poor-must agitate, vibrate	1.35-1.45
Very poor-requires agitation	1.46-1.59
Very very poor-special, agitation of hoper required	>1.60

4.3.5 HYGROSCOPICITY (%H):

The hygroscopicity of a powder is its equilibrium moisture content after being exposed to air humidity under given conditions. It was determined by calculating the increase in sample weight after being kept in a humidifier at ambient relative humidity of 76 ±2% and a temperature of 22± 2^0C for 24 h.

Procedure: The saturated solution of Ammonium chloride / Ammonium sulfate was prepared and sample of 50 ml was taken in a dessicator to maintain humidity of 75 ±2%.

Weight of empty stoppered Petri plate is **m1**

Weight of empty stoppered Petri plate + drug sample is **m2**

The petri plate is unstoppered and placed in dessicator containing Ammonium chloride solution and kept for 24 hrs.

Weight of empty stoppered Petri plate + drug sample after 24 hrs is **m3**

m3 – m2/ m2 – m1 *100

Table 10: HYGROSCOPICITY

HYGROSCOPICITY	WEIGHT GAIN
Slight hygroscopic	0.0 -0.12%
Hygroscopic	0.12 -2%
Very hygroscopic	2- 15%
Deliquescent	>15%

4.3.6 STABILITY STUDIES:

4.3.6.1 FT-IR SPECTRAL STUDIES:

The IR spectra for the formulation excipients and pure drugs were recorded on FTIR spectrophotometer using KBr palette technique (1:100) at the resolution rate of $4cm^{-1}$. Spectrum was integrated in transmittance mode at the wave number range 400-4000 cm^{-1}

4.3.6.2 MICROBIOLOGICAL GROWTH STUDY OF ALL POLYMERS AND DRUGS:

100 mg of the polymer sample were separately aseptically mixed with 9 ml of sterile normal saline and the PH was adjusted to 7. 1ml of dispersion was mixed with 20 ml of sterile lactose broth and placed separately in Petri dish. And the plates were incubated at 37±1oC for 24 hr. After incubation period the samples were observed for the presence of micro flora.

4.3.6.3 Thermal stability

Megesterol acetate powder was exposed to different temperature in an oven for 24 h.

Table 11 Thermal stability

S.No	Temperature
1	0^0c
2	10^0c
3	20^0c
4	30^0c
5	40^0c
6	50^0c
7	60^0c

4.3.7ANALYTICAL METHOD DEVELOPMENT:

Megesterol acetate can be estimated by various methods such as HPTLC, UV spectrophotometry, HPLC etc. In the present investigation, Megesterol acetate was estimated by UV/VIS spectrophotometer.

4.3.7.1 Preparation of stock solution:

Megesterol acetate (25mg) was accurately weighed and transferred into the 25 ml volumetric flask. It was dissolved in acetonitrile and volume was made up to the mark with acetone to get a 1000 ug/ml solution (Stock A). From this 1 ml was pipette out and then diluted up to 100 ml with 1% SLS to get a stock solution of 10µg/ml (Stock B).

From the stock B solution 2, 4, 6,8and 10 ml were transferred to 10 ml volumetric flasks and diluted with the 1% SLS, up to the mark to obtain Megesterol acetate concentration of 2, 4,6,8and 10µg/ml respectively.

4.4 FORMULATION DEVELOPMENT OF MEGESTEROL ACETATE:

4.4.1.1. Solid dispersion of Megesterol acetate with PEG 6000 by solvent evaporation tehnique:

This method involves dissolving drug and carrier in a common organic solvent and then evaporating the solvent, the carrier taken is PEG 6000. The solid dispersions are prepared by solvent evaporation at weight ratios 1:1, 1:2, 1:3, 1:4, 1: 5 for megesterol and PEG 6000. The appropriate amount of megesterol and PEG 6000 were dissolved in acetonitrile with continous stirring. Than the solvent was evaporated at ambient temperature and kept in dessicator for 24 hrs, then powdered in a mortar and sieved through 60 mesh screen and stored at ambient temperature for further use.

Table 12 Composition of solid dispersion of megesterol acetate with PEG 6000:

S. No	Megesterol : PEG 6000	Batch code
1	1:1	SP1
2	1:2	SP2
3	1:3	SP3
4	1:4	SP4
5	1:5	SP5

4.4.1.2. Formulation of megesterol acetate tablets using superdisintegrants by Direct Compression:

1. **Weighing & Sifting:** Solid dispersion, superdisintegrants (sodium starch glycolate, cross povidone XL10) and all other ingredients except lubricants were accurately weighed and sifted through # 40 mesh.
2. **Mixing and blending:** Step 1 materials were mixed and blended in a mortar.
3. **Lubrication:** Talc, magnesium stearate was accurately weighed and sifted through #60 mesh. Step 2 materials were blended with lubricants for 2 min.
4. **Compression:** The final blend was compressed into tablets with 7.5mm tooling set

Table13: Composition of Megesterol acetate with PEG6000 by dry granulation technique

Super Disintegrants	Sodium starch glycolate					Crosspovidone XL10		
Formula	F1mg	F2mg	F3mg	F4mg	F5mg	F6mg	F7mg	F8mg
Solid dispersion	SP1 (40)	SP2 (60)	SP3 (80)	SP4 (100)	SP5 (120)	SP1 (40)	SP2 (60)	SP3 (80)
SSG	9	9	9	9	9	--	--	--
CrosspovidoneXL10	--	--	--	--	--	9	9	9
Mannitol	18.75	18.75	18.75	18.75	18.75	18.75	18.75	18.75
Avicel pH 102	227.75	207.75	187.75	167.75	147.75	227.75	207.75	187.75
Talc	3	3	3	3	3	3	3	3
Mg. stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total weight	300	300	300	300	300	300	300	300

4.4.2. Hydrotropic approach:

Initially solubility of Megesterol acetate was determined individually in solutions of 4 hydrotropic agents (Ha) namely urea (U), sodium acetate (A), sodium benzoate (B), sodium citrate (C) at concentration of 10%, 20%, 30% and 40% solutions using purified water as solvent. For determining solubility, accurately measured 3 ml of particular hydrotropic agent was taken in a 10 ml volumetric flask and excess amount of drug was added and mechanically shaken until saturated solution was formed. The volumetric flask was shaken on mechanical shaker for 12 h so that equilibrium solubility can be achieved and solution was allowed to equilibrate for 24 h. Then solution was centrifuged at 2000 rpm for 5 min in ultra-centrifuge and then solution was filtered through whatmann's grade 41 filters. Aliquot was suitably diluted with purified water and analyzed using UV spectrophotometer at 292 nm.

Table 14: composition of hydrotropic agents

Ingredients	formulation	concentration
Sodium acetate	F9	10%
	F10	20%
	F11	30%
	F12	40%
Sodium benzoate	F13	10%
	F14	20%
	F15	30%
	F16	40%
Sodium citrate	F17	10%
	F18	20%
	F19	30%
	F20	40%
Urea	F21	10%
	F22	20%
	F23	30%
	F24	40%

4.4.2.1Mixed Hydrotropy:

Table 15: composition of hydrotropic agents in combination

Ingredients	Sodium acetate	Sodium benzoate	Sodium citrate	Urea	Total %
F25	20	--	--	20	40%
F26	--	20	--	20	40%
F27	--	--	20	20	40%
F28	20	20	--	--	40%
F29	20		20		40%
F30		20	20	--	40%
F31	5%	15%	20%	--	40%
F32	15%	20%	5%	--	40%
F33	20%	5%	15%	--	40%
F34	10%	10%	20%	--	40%
F35	10%	20%	10%	--	40%
F36	20%	10%	10%	--	40%
F37	--	15%	20%	5%	40%
F38	--	20%	5%	15%	40%
F39	--	5%	15%	20%	40%
F40	--	10%	20%	10%	40%
F41	--	20%	10%	10%	40%
F42	--	10%	10%	20%	40%

4.4.2.2. Preparation of solid dispersions of Megesterol Acetate with hydrotropic agents by physical mixing method:

For preparation of solid dispersion with optimized hydrotrope concentration, accurately weighed Urea, sodium benzoate, sodium citrates were taken in a mortar and were mixed properly, then megesterol acetate was added to the above blend and thoroughly

triturated for 5min. The solid dispersion thus obtained was passed through sieve # 60 and were finally stored in an airtight glass bottle.

Table 16: composition of solid dispersion of Megesterol acetate and hydrotropic agents

Drug	Hydrotropic agents		
Megesterol Acetate	Urea	Sodium benzoate	Sodium acetate
Equivalent wt 20 mg	10%	10%	20%

4.5-Pre compression studies:

4.5.1-Angle of Repose:

The angle of repose of granules was determined by the funnel method. The accurately weighed granules/ powder were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation:

$$\tan \theta = h/r \quad (1)$$

Where h and r are the height and radius of the powder cone.

4.5.2-Bulk Density & Tapped density:

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 1g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2-second intervals. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following formulas.

LBD = weight of the powder/volume of the packing (2)

TBD = weight of the powder/ tapped volume of the packing (3)

4.5.3. Compressibility Index:

Compressibility index of the granules was determined by Carr's compressibility index

$$\text{Carr's Index (\%)} = [(\text{TBD-LBD}) \times 100] / \text{TBD}$$

4.5.4. Drug content evaluation:

100 mg equivalent weight of sample was weighed and add suitable medium and made up to 100 ml with medium. 1ml of this solution is made up to 100 ml with buffer. Drug content was estimated by an UV spectrophotometric method based on the measurement of absorbance at particular nm.

4.6-Evaluation of tablets:

4.6.1-Weight variation:

Twenty tablets were weighed individually and the average weight was determined. Then percentage deviation from the average weight was calculated. Deviation should not exceed the values given in table

Table 17: Standard limit value in weight variation test

Average weight of a tablet	Percentage Deviation
80 mg or less	±10
>80 and <250mg	±7.5
250mg or more	±5

4.6.2-Hardness:

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling the hardness of the tablets was determined using Pfizer hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and hardness of the tablets was determined.

4.6.3-Friability:

Roche Friabilator was used for testing the friability. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm. After 4 min., the tablets were weighed and the percentage loss in tablet weight was determined.

$$\% \text{ loss} = \frac{\text{Initial wt. of tablets - Final wt. of tablets}}{\text{Initial wt. of tablets}} \times 100$$

4.6.4-Tablet thickness:

Thickness was measured using a calibrated screw gauge. Three tablets of each formulation were picked randomly and thickness was measured individually.

4.6.5. In Vitro Disintegration Test

The test was carried out on 6 tablets using digital tablet disintegration tester (Veego, India). 1% SLS solution at 37°C ± 2°C was used as a disintegration media, and the time taken for complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured in seconds.

4.6.6. Wetting Time

A Petri dish containing 6 ml of distilled water was taken. A tablet containing a small quantity of amaranth color was placed on it. Time required for the upper surface of the tablet to become complete red was noted.

4.6.7-Drug content:

Ten tablets were weighed and powdered and required mg equivalent weight of drug was accurately weighed and transferred into a 100 ml volumetric flask. It was dissolved and made up the volume with medium. Subsequently the solution in volumetric flask was filtered and

suitable dilutions were made and analyzed at particular nm using UV-Visible spectrophotometer. The drug content of each sample was estimated from standard curve of drug using particular medium.

4.6.8-In vitro drug release:

The USP paddle method was adopted in this study. The release medium consisted of 900 ml of 1% SLS. A known quantity from each batch of the Megesterol acetate were placed in appropriate chamber of the release apparatus and agitated at 50 rpm. At predetermined time intervals, 10 ml of the release medium was withdrawn, appropriately diluted and absorbance determined at a wavelength of 249 nm using UV spectrophotometer. The volume of the release medium was kept constant by replacing it with 10ml of fresh buffer medium after each withdrawal.

CHAPTER 5

INVESTIGATIONAL REPORTS

5.1 PRE-FORMULATION STUDIES:

5.1.1 Identification of Megesterol Acetate:

PARAMETRE	STANDARD VALUE	OBSERVED VALUE
Description	Crystalline powder	Crystalline powder
Odor	Odor less	Odor less
Colour	White	White
Solubility	Practically insoluble in water, sparingly soluble in alcohol; soluble in acetone; very soluble in chloroform	Practically insoluble in water, sparingly soluble in alcohol; soluble in acetone; very soluble in chloroform
Melting point	213-220 ^{o}C	214 ^{o}C
Percentage purity	99%	98.9%

Table 18: Identification of Megesterol Acetate

5.1.2. Thermal degradation:

Temperature	Initial concentration	Concentration after 3 hr
40˚C	0.3291	0.430
60˚C	0.3291	0.191

Table no.19. Thermal degradation

5.1.3. Flow properties of Megesterol Acetate:

PARAMETRE	OBSERVED VALUE
Angle of repose	31.37^0
Bulk density	0.386 gm/cc
Tapped density	0.678 gm/cc
Cars index %	43.103 %
Hausner`s ratio	1.75
Drug content	97%
Particle Shape & Size	Cube shape crystals, 15.29 um

Table 20: Flow properties of Megesterol Acetate

5.1.4. Solubility of API in different solvents

Solubility of API (%)				
Time Intervals (nm)	Water + 0.5% SLS	Water + 1% SLS	pH 1.2 (USP) + 1% SLS	pH 4.5 (USP) + 1% SLS
15	46.1	74.8	60.7	75.6
30	58.5	84.1	70.7	99.6
60	60.9	93.7	83.6	-
120	63.5	-	88.8	-

Table:21 Solubility of API in different solvents

5.1.5 Partition Co-efficient:

The Partition Co-efficient value obtained from hexane to water is 4.569

5.1.6. Hygroscopicity:

It is evident by no change in the weight of the sample at higher moisture level of 75% RH even after 168 hrs and at the same time powder is not stick to the Petri dish and is free flowing.

Table 22: Hygroscopicity of Megesterol acetate

Temp / Humidity	Observation after 168 hrs	Megesterol acetate (API)
25°C / 29 RH	% Moisture pick up (Maximum)	0.175
25°C / 43 RH	% Moisture pick up (Maximum)	0.238
25°C / 75 RH	% Moisture pick up (Maximum)	0.085

5.2. MICROBIAL TESTING OF DRUG AND POLYMERS:

Fig: 3 Megesterol Acetate

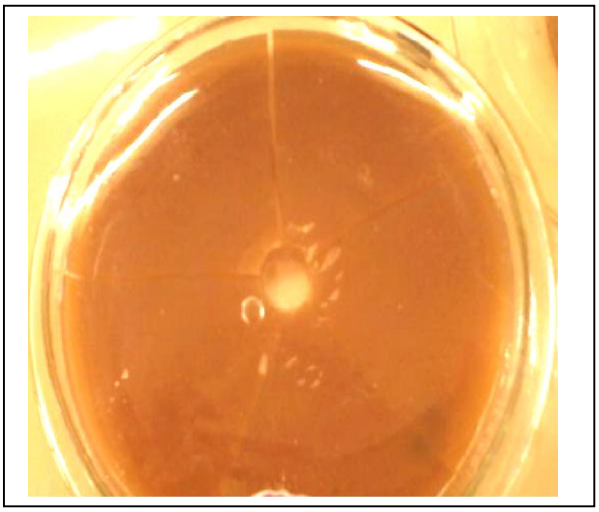


Fig : 4 Megesterol Acetate with PEG 6000

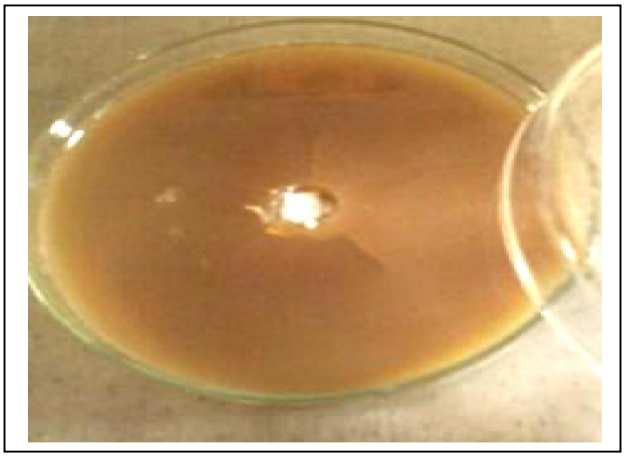


Fig: 5 Megesterol with SSG

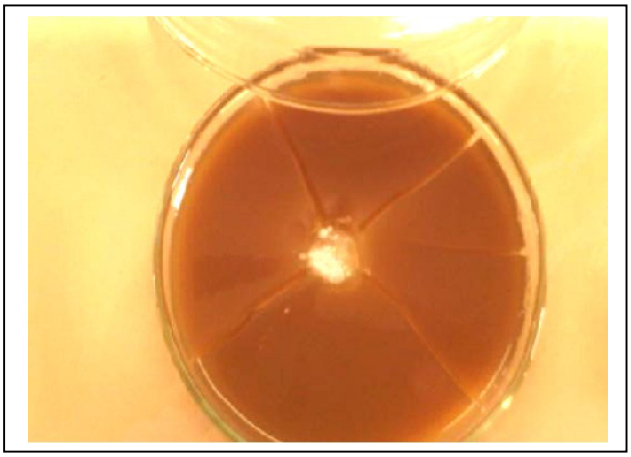


Fig : 6 Megesterol with Crosspovidone XL10

Microbial testing of drug and polymer

5.3 ANALYTICAL METHOD DEVELOPMENT

5.3.1. Analytical methods for estimation of Megesterol acetate by UV/VIS Spectrophotometer

Concentration(X) (µg / ml)	Absorbance (Y)
2	0.170
4	0.368
6	0.543
8	0.729
10	0.891

Table 23: Analytical methods for estimation of Megesterol acetate

5.3.2. Standard Calibration Curve of Megesterol acetate:

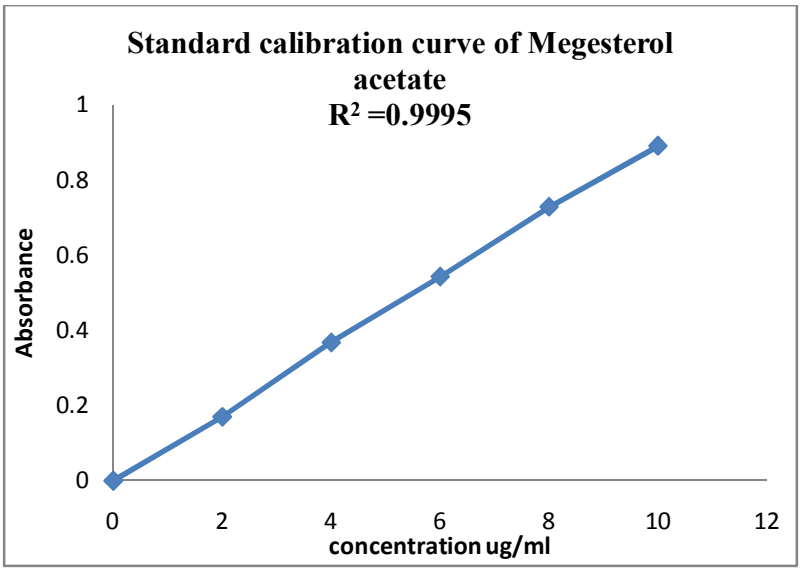


Fig no: 7 Standard Calibration Curve of Megesterol acetate

5.4. STABILITY STUDIES

FT IR Spectral studies:

Fig no. 8 IR Studies of Megesterol acetate

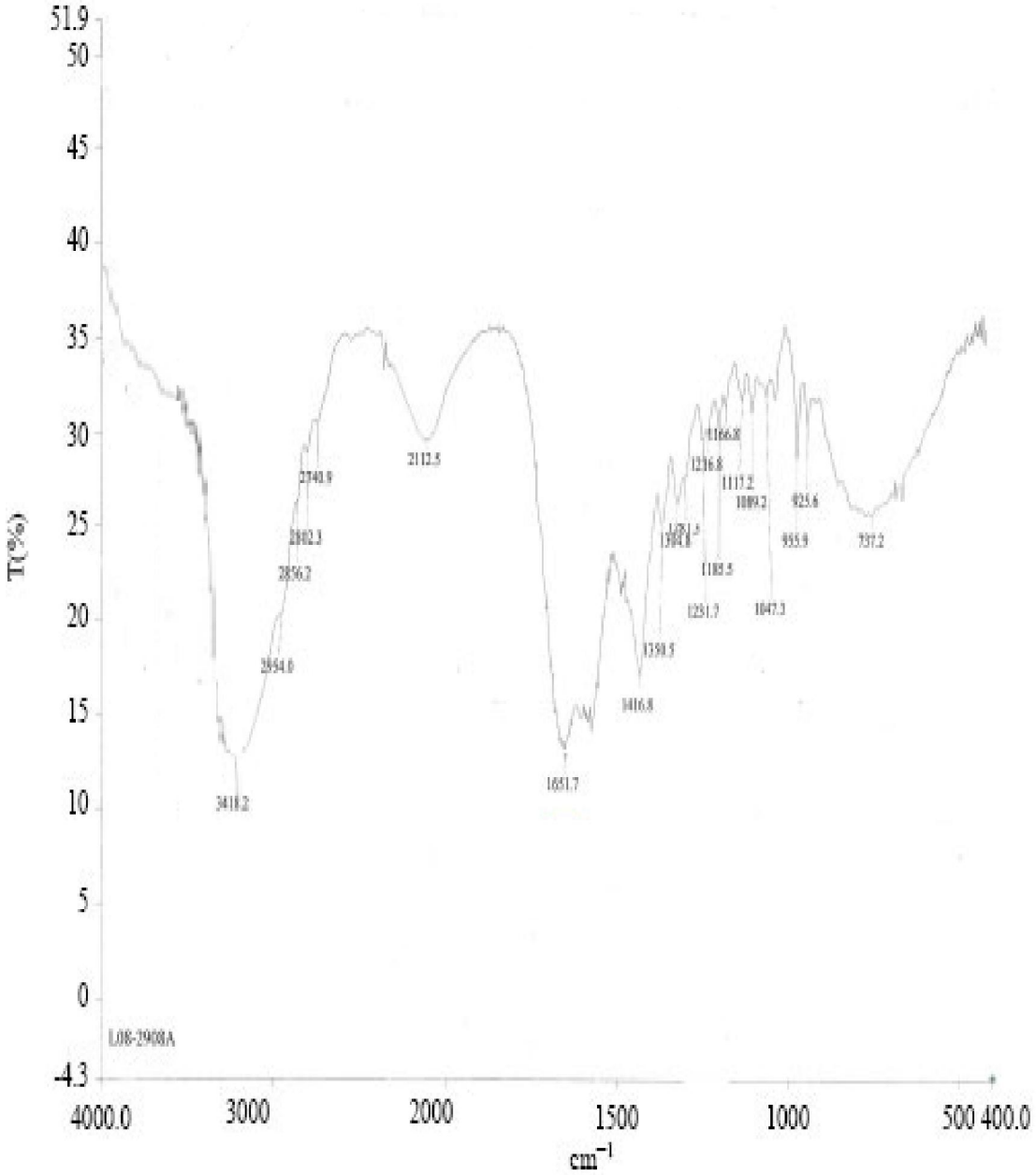


Fig no.9 IR Studies of Drug + PEG 6000

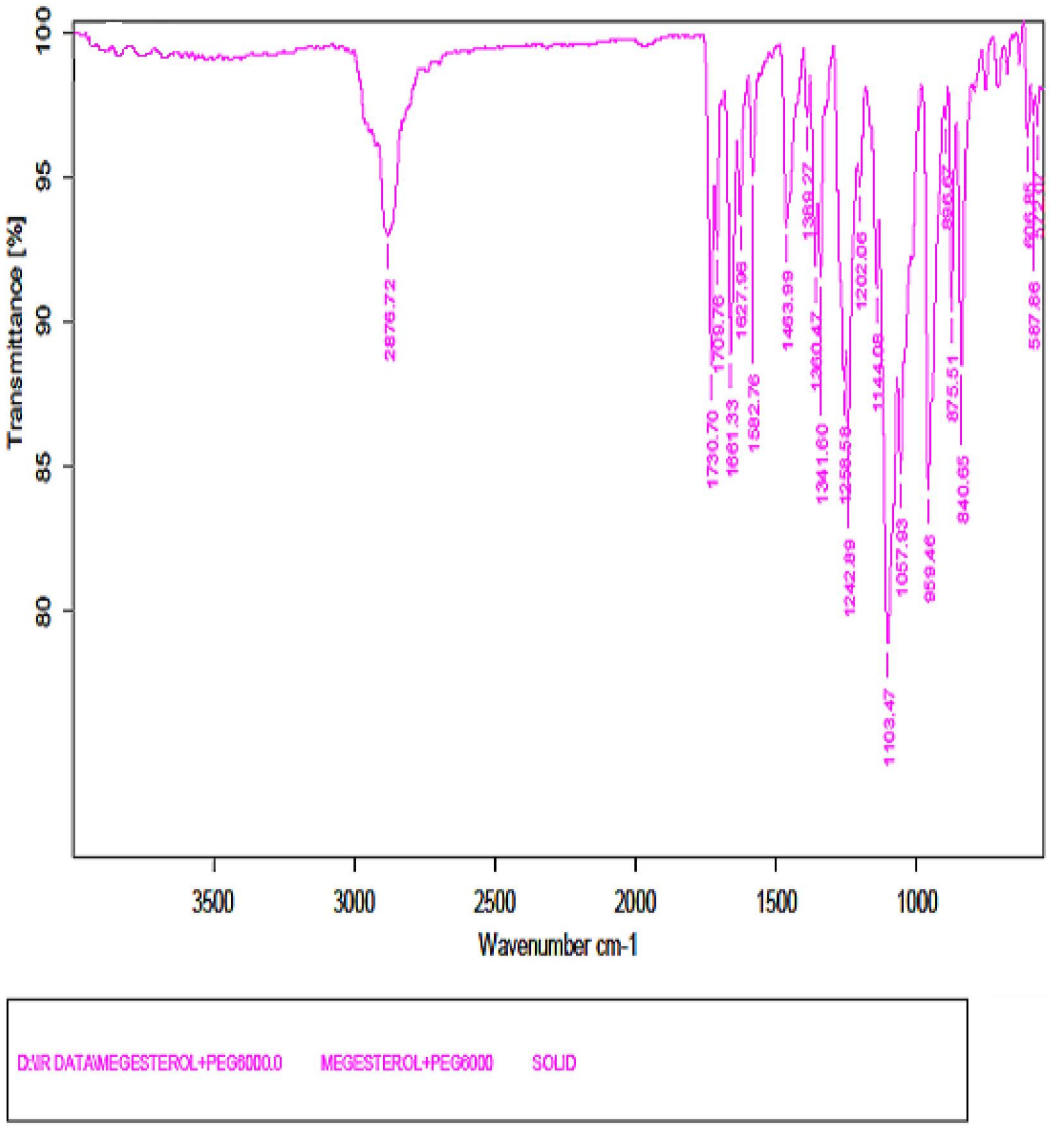


Fig no.10 IR Studies of Drug + Avicel pH 102

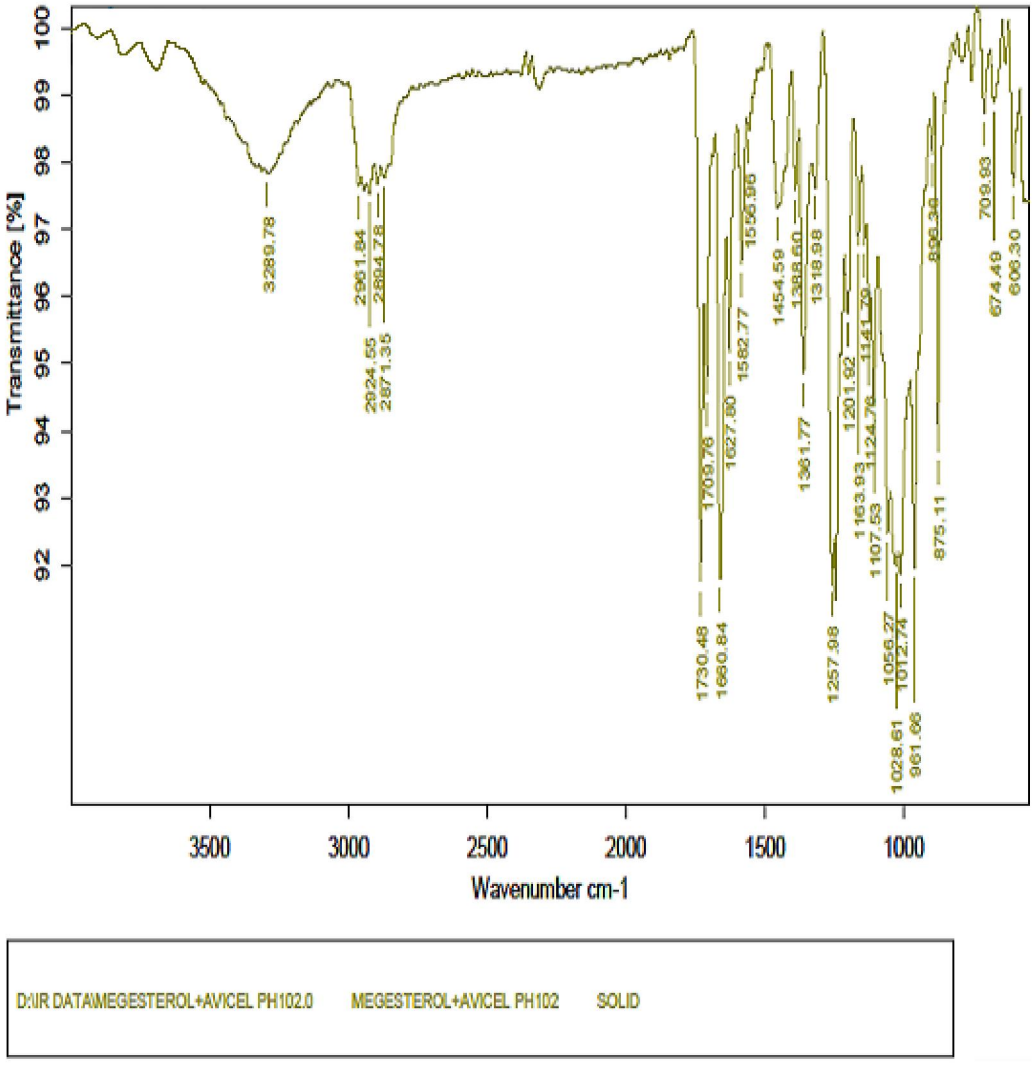


Fig no.11 IR Studies of Drug + sodium acetate

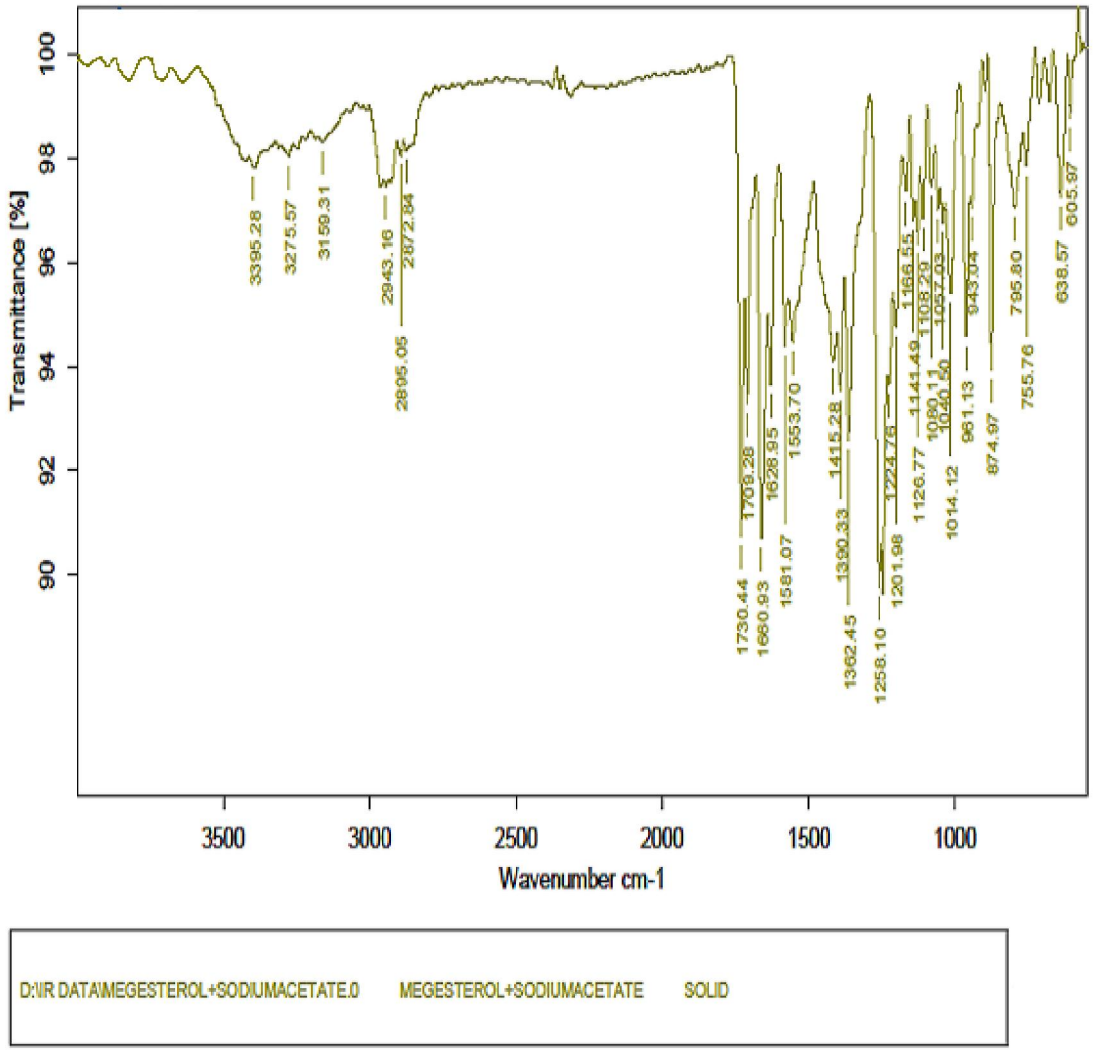


Fig no.12 IR Studies of Drug + sodium benzoate

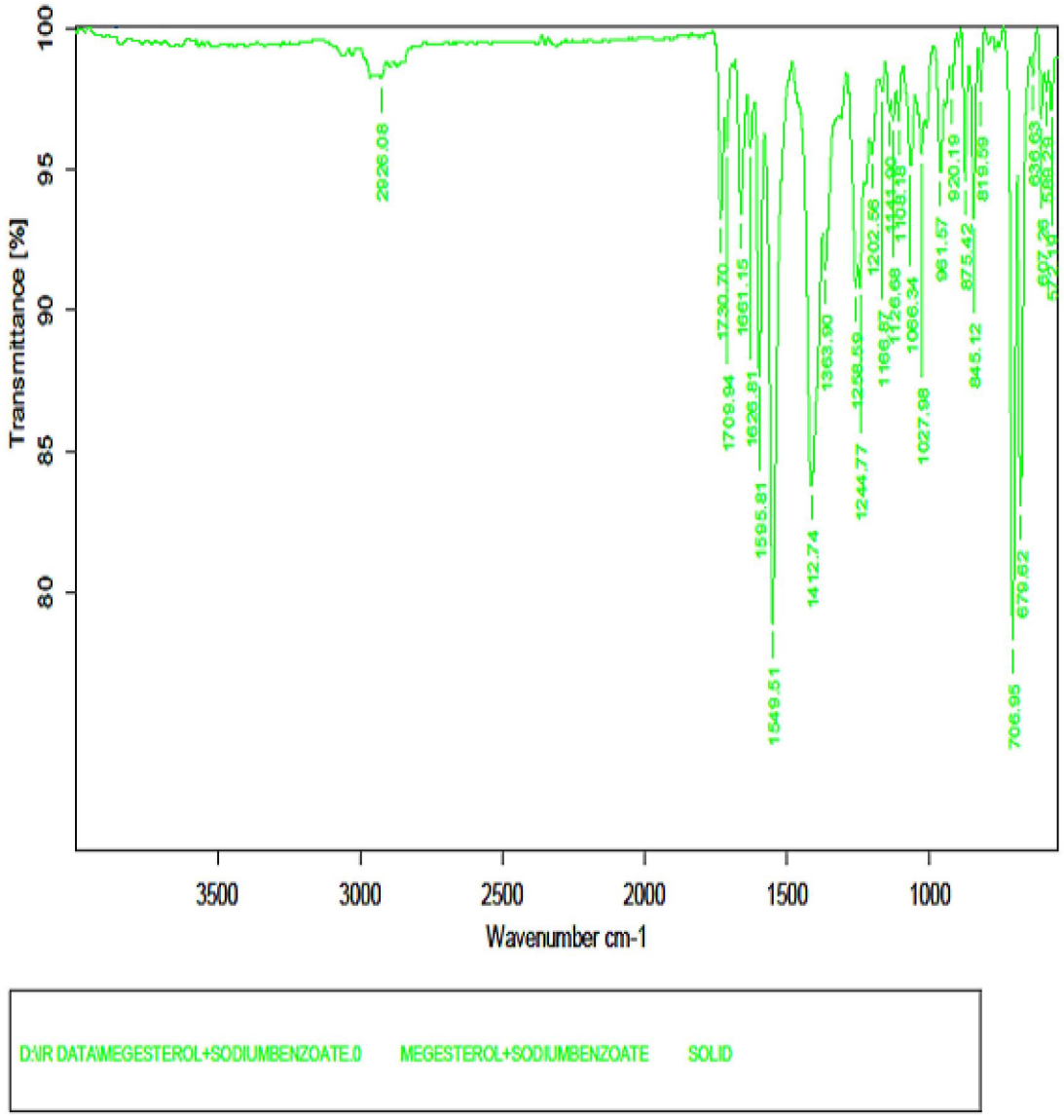
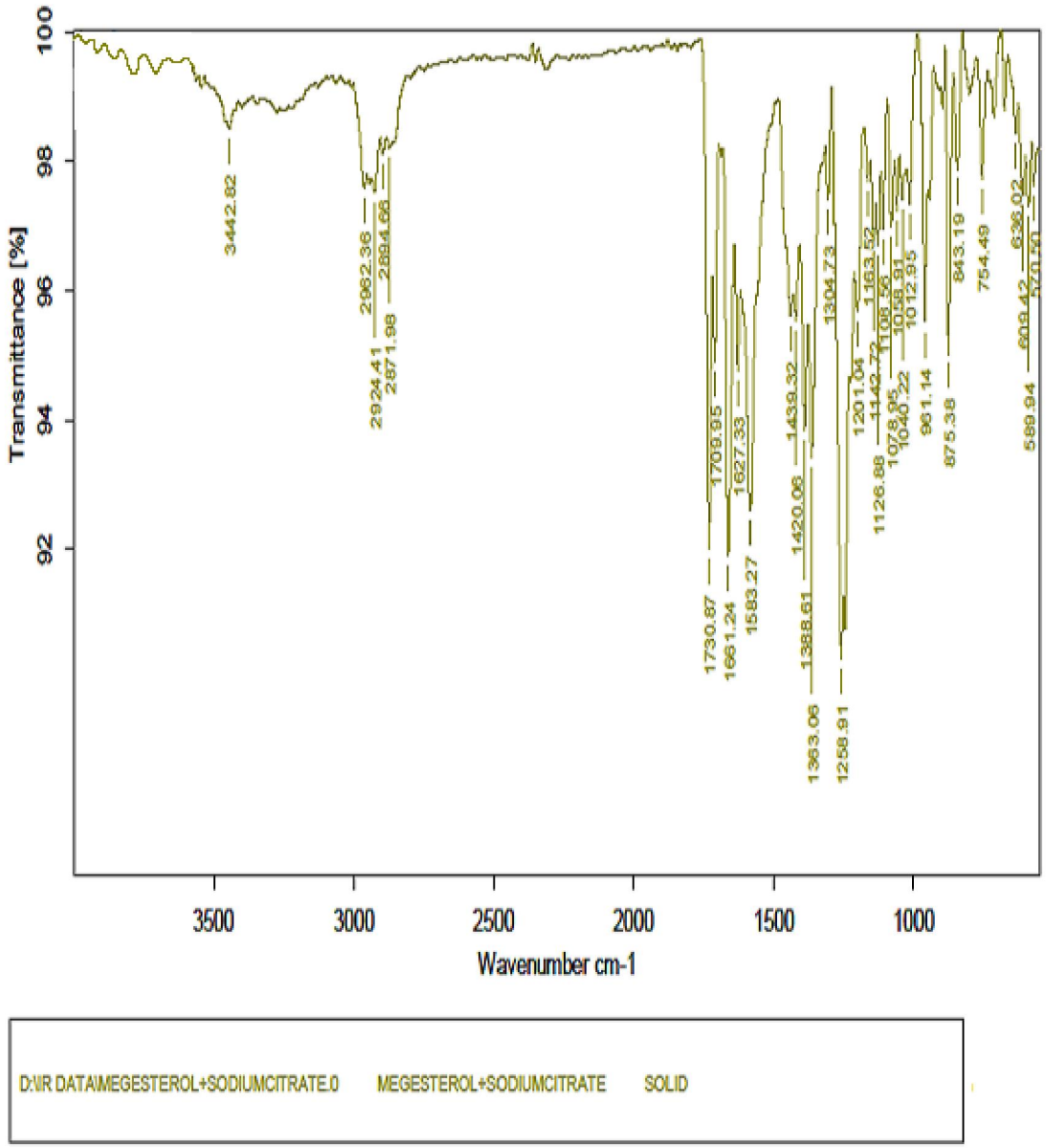


Fig no.13 IR Studies of Drug + sodium citrate



5.5. EVALUATION OF PRE- COMPRESSION PARAMETRES:

Tabl e 24: Characterization of Megesterol Acetate powder Formulated with Citric acid:

Formula	Angle of repose	BD (g/cc)	TD (g/cc)	Carr's index (%)	Hausners ratio	Drug content (%)
F1	25.4^0	0.68	0.72	9.55	1.15	97.5
F2	25.5^0	0.67	0.710	9.6	1.17	95.5
F3	25.2^0	0.64	0.708	8.5	1.06	96.5
F4	24.4^0	0.62	0.690	10.1	1.058	98.2
F5	26.4^0	0.68	0.732	9.1	1.09	97.5
F6	24.5^0	0.60	0.71	10.8	1.09	95.5
F7	23.2^0	0.69	0.75	11.1	1.18	96.5
F8	23.4^0	0.70	0.74	11.4	1.20	98.2

Table 25: Post compression studies of Megesterol Acetate tablets with Superdisintegrants:

Formulation	F1	F2	F3	F4	F5	F6	F7	F8
Hardness (kg/cm^2)	4.5±1.0	4.5.0±1.02	4.0±1.02	4.5±1.08	4.0±1.02	4.5±1.02	4.0±1.0	4.5±1.02
Friability (%)	0.62±0.01	0.55±0.02	0.58±0.01	0.55±0.05	0.60±0.01	0.65±0.02	0.59±0.01	0.52±0.02
Weight Variation (mg)	298±0.7	299±0.5	299±0.8	298.5±0.2	299±0.1	298.7±0.2	299.2±0.1	298.9±0.7
Thickness (mm)	2.60	2.3	2.4	2.35	2.4	2.42	2.38	2.4
Drug Content	96.5±0.2	97±0.5	97.8±0.6	98±0.5	97±0.5	98.9±0.2	98±0.5	98.5±0.1
Disintegration time (sec)	65±0.6	62±0.4	75±0.2	76±0.4	82±0.2	54±0.7	42±0.2	34±0.5
Wetting time(sec)	214±0.9	175±0.85	57±1.04	49±0.5	46±0.6	35±1.0	42±0.2	34±0.5

Table no. 26. Dissolution studies of Megesterol acetate with SSG &Crosspovidone

Time (min)	% Drug release in the formulations								
		Sodium Starch Glycolate					Crosspovidone		
	Puredrug	F1 (1:1)	F2 (1:2)	F3 (1:3)	F4 (1:4)	F5 (1:5)	F6 (1:1)	F7 (1:2)	F8 (1:3)
0	0	0	0	0	0	0	0	0	0
10	2.13	10.8	12.9	16.75	13.1	12.8	26.2	18.85	17.5
20	3.5	27.8	23.6	32.39	26.2	22.8	95.8	72.5	73.6
30	4.77	40.17	36.6	58.9	49.4	38.13		90.2	80.2
40	6.54	48.8	47.9	79.55	69.6	47.02			82.5
50	6.8	66.1	73.8	89.9	78.5	71.6			85.8
60	6.48	78.5	85.6.5		87.9	86.5			

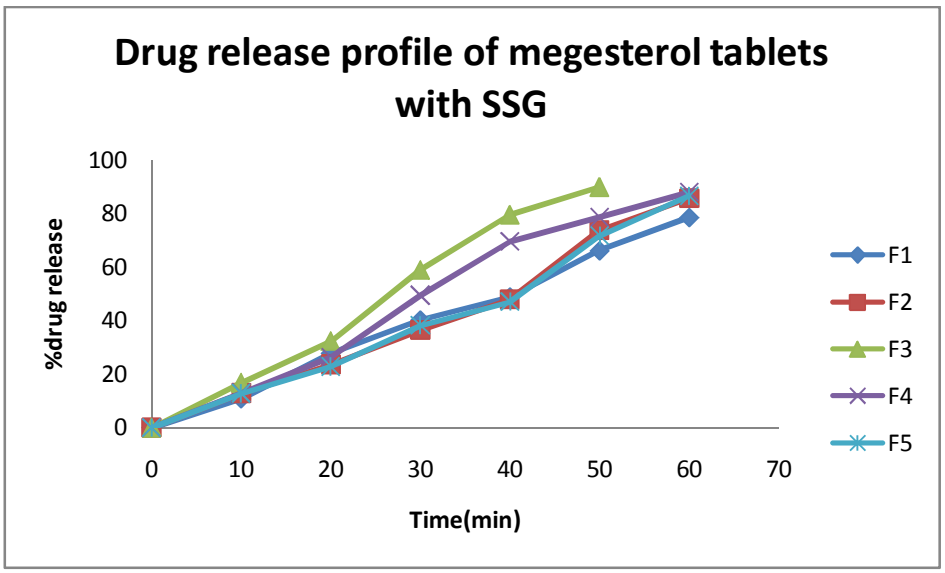


Fig no. 14 drug release profile of Megesterol tablets with SSG

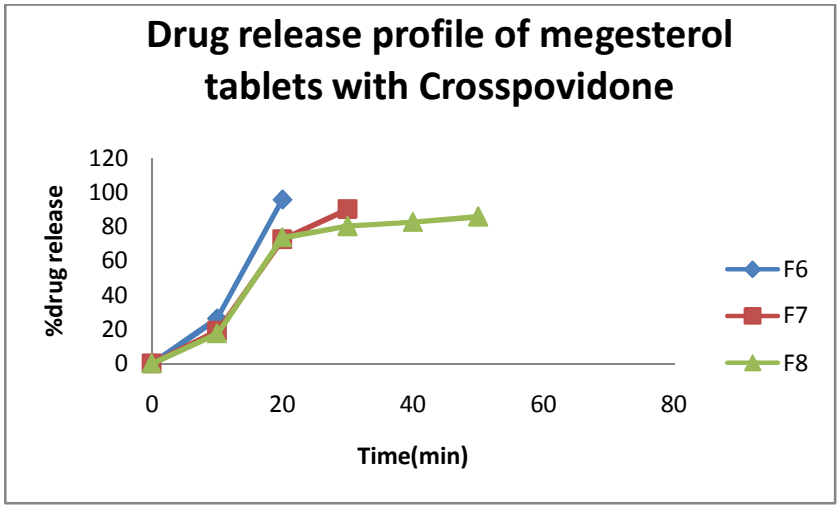


Fig no. 15 drug release profile of Megesterol tablets with Crosspovidone

5.5.1. First order graph of Megesterol tablets with SSG

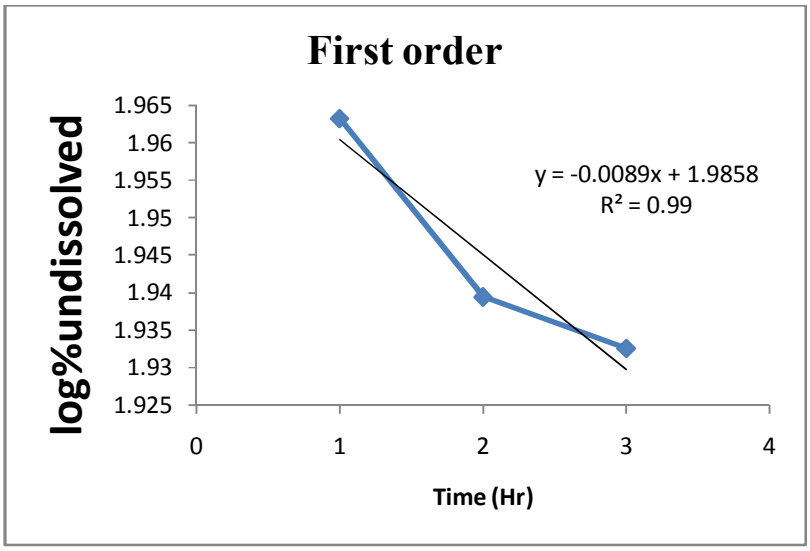


Fig no.16 First order graph of Megesterol tablets with SSG

5.5.2. First order graph of Megesterol tablets with Crosspovidone

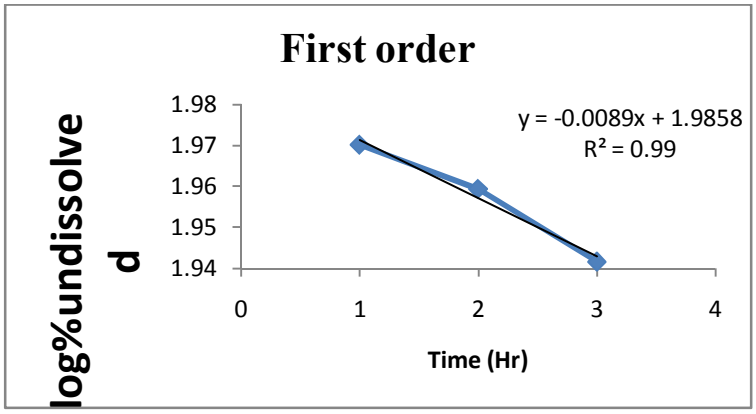


Fig no. 17. First order graph of Megesterol tablets with Crosspovidone

5.6. HYDROTROPY:

Table no. 27. Solubility studies of Megesterol with different Hydrotropic agents

Ingredients	formulation	concentration	Solubility in mg/ml
Sodium acetate	F9	10%	0.00439
	F10	20%	0.00491
	F11	30%	0.00541
	F12	40%	0.00849
Sodium benzoate	F13	10%	0.029
	F14	20%	0.0472
	F15	30%	0.079
	F16	40%	0.98
Sodium citrate	F17	10%	0.00826
	F18	20%	0.446
	F19	30%	0.544
	F20	40%	0.886
Urea	F21	10%	0.0098
	F22	20%	0.011
	F23	30%	0.039
	F24	40%	0137

5.6.1. Mixed hydrotropy:

Table. 28. Solubility studies of Megesterol with different Hydrotropic agents in combination

Ingredients	Sodium acetate	Sodium benzoate	Sodium citrate	Urea	Total %	Solubility in mg/ml
F25	20	--	--	20	40%	0.0174
F26	--	20	--	20	40%	0.0182
F27	--	--	20	20	40%	0.0914
F28	20	20	--	--	40%	0.195
F29	20		20		40%	0.0176
F30		20	20	--	40%	0.222
F31	5%	15%	20%	--	40%	0.639
F32	15%	20%	5%	--	40%	1.143
F33	20%	5%	15%	--	40%	0.3358
F34	10%	10%	20%	--	40%	1.195
F35	10%	20%	10%	--	40%	0.242
F36	20%	10%	10%	--	40%	0.347
F37	--	15%	20%	5%	40%	6.099
F38	--	20%	5%	15%	40%	1.0806
F39	--	5%	15%	20%	40%	1.004
F40	--	10%	20%	10%	40%	9.14
F41	--	20%	10%	10%	40%	6.96
F42	--	10%	10%	20%	40%	0.688
F43	10	10	10	10	40%	1.008

5.6.2. Drug release profile of Megesterol acetate tablets using hydrotropic agents:

Table no. 29.% of drug release of Megesterol acetate tablets using hydrotropic agents

Time (min)	% Drug release			
	F16(B)	F30(A+B)	F34(A+B+C)	F40(U+B+C)
10	9.87	13.75	22.40	36.71
20	14.34	21.32	35.93	98.34
30	22.90	38.02	52.06	103.06
40	39.21	42.21	70.32	
50	56.86	65.84	98.21	
60	68.93	78.23	102.3	

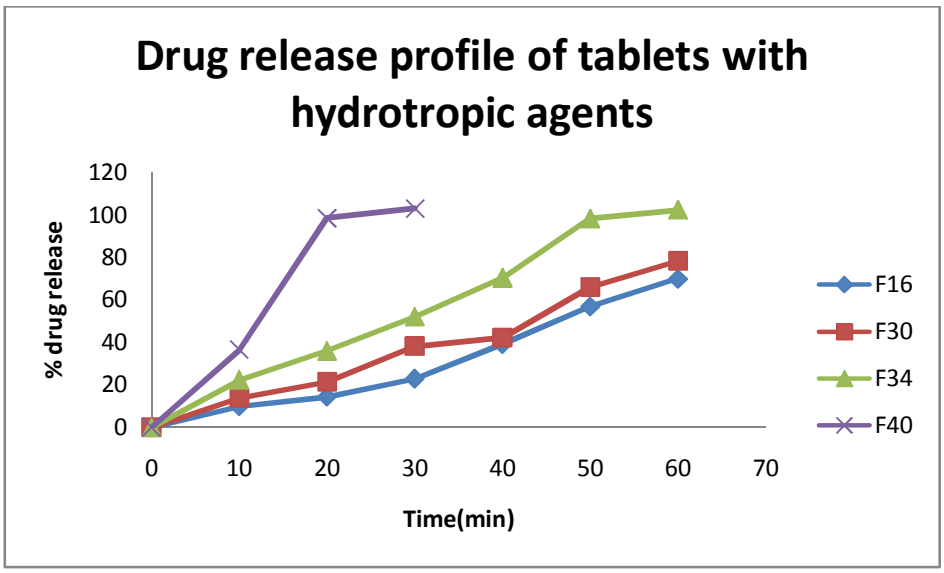


Fig no. 18. Drug release profile of Meg. Acetate tablets with hydrotropic agents

5.6.3. First order graph of Megesterol tablets with hydrotropic agents

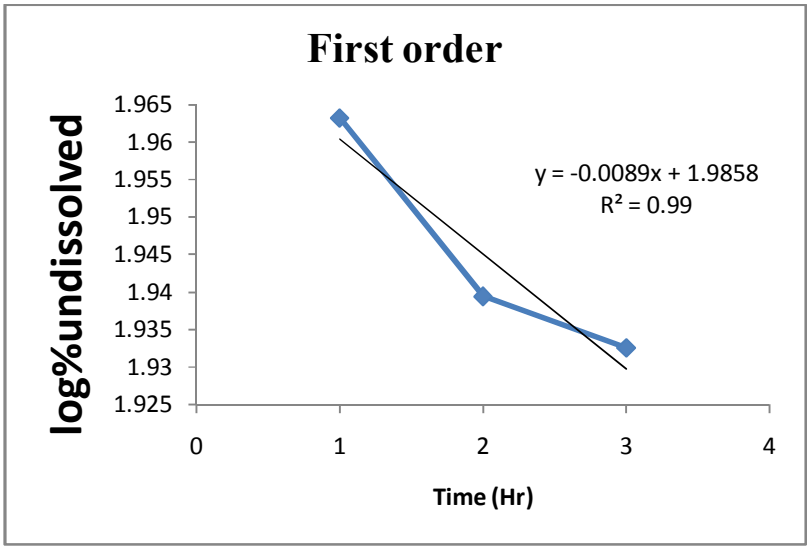


Fig no.19 First order graph of Megesterol tablets with hydrotropic agents

5.6.4. Comparision of Drug release profile of Megesterol acetate solid dispersion using hydrotropic agents with innovator:

TIME (min)	Solid dispersion with hydrotropic agents			Innovator
	F30(A+B)	F34(A+B+C)	F40(U+B+C)	Megrace Tablets
2	13.75	22.40	36.71	16
4	21.32	35.93	98.34	32.3
6	38.02	52.06	98.96	51.8
8	42.21	70.32		79.6
10	65.84	98.21		99.8
12	78.23	102.3		

Table 30: Comparision of Drug release profile of Megesterol acetate solid dispersion using hydrotropic agents with innovator

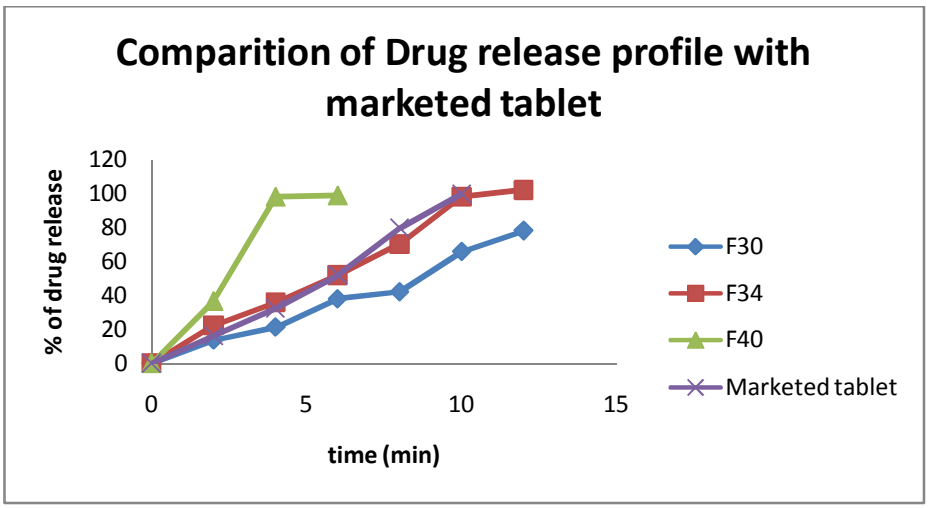


Fig no.20 Comparision of Drug release profile of Megesterol acetate solid dispersion using hydrotropic agents with innovator

CHAPTER-6

RESULTS AND DISCUSSION

Megesterol acetate is an antineoplastic and progestational drug used in the treatment of breast cancer which belongs to BCS class II, which exhibits low aqueous solubility and high membrane permeability that leads to poor bioavailability. Hence in the present study solid dispersion technique and mixed hydrotropic techniques were used to enhance the solubility of Megesterol acetate. The following preformulation studies were conducted for the generation of useful information for the formulation development of most stable dosage form.

Preformulation studies:

The solubility of Megesterol acetate was determined in different solvents like water, alcohol, acetone and chloroform. It was found to be practically insoluble in water, sparingly soluble in alcohol, soluble in acetone, very soluble in chloroform. Form the solubility analysis studies megestro acetate was found to be poorly soluble drug and to enhance the solubility solid dispersion technique and mixed hydrotropic techniques were used in the formulation development.

Micromeritic properties:

Characterization of Megesterol acetate was conducted by different parameters and the reports were shown in the above table 24. The studies on angle of repose showed 25±1.5 values indicating good flow properties. On analyzing for density it was found that megesterol acetate showed bulk density value 0.68 gm/cc, tapped density value 0.78 gm/cc. Carr's Index value is 9-11 % which indicates good flow properties. Hausner's ratio of megesterol acetate was found to be 1.12-1.18 which indicates good flow properties. Based on the above results

Megesterol acetate was found to have good flow properties. Hence, direct compression method was used for the formulation of tablets.

Formulation development:

Megesterol acetate tablets were formulated as fast release tablets by using two different super disintegrants namely Sodium starch glycolate and Crosspovidone XL 10 from F1 to F8. PEG 6000 is used as carrier. The solid dispersions are prepared by solvent evaporation at weight ratios 1:1, 1:2, 1:3, 1:4, and 1: 5 for megesterol and PEG 6000. As the concentration of PEG 6000 increased the % of drug release also increased upto 1:3 ratio and then upon increase in the conc. the drug release decreased.

Megesterol acetate fast dissolving tablets were formulated by using different hydrotropic agents like urea, sodium benzoate, sodium acetate, sodium citrate from F9 to F43. From F9 to F24 four hydrotropic agents were used individually at a concs of 10%, 20%, 30% and 40% to increase the solubility of Megesterol acetate. From F25 to F30 a combination of two hydrotropic agents are used at a conc. of 20% each to get total concentration of 40%. From F31 to F40 a combination of three different hydrotropic agents were used at different concentrations to get total concentration of 40%. From these formulations F16, F30, F34 and F40 are optimized based on better solubility. These formulations are formulated into fast release tablets.

Effect of solid dispersion:

To enhance the solubility of Megesterol acetate solid dispersions were prepared by using PEG 6000 as a carrier in different ratios (1:1, 1:2, 1:3, 1:4, and 1: 5) by solvent evaporation technique. As the conc. of PEG 6000 increased the % drug release increased up to 1:3 ratio then onwards the % drug release decreased in the formulation with SSG. In the formulation

with Crosspovidone, drug and PEG 6000 at a ratio of 1:1 showed better drug release. Megesterol acetate tablets with solid dispersions showed enhanced solubility compared to the tablet without solid dispersions.

Effect of mixed hydrotropic technique:

As the concentration of hydrotropic agent increased from 10% to 40% the solubility was enhanced, this increase in the solubility is shown in the table no.27. As the number of hydrotropic agents increased the solubility was enhanced and this increase in the solubility is shown in the table no.28. Megesterol acetate solid dispersions were prepared and this was formulated into tablet by including hydrotropic agents in the formulation.

Drug release studies:

Drug release studies were conducted for Megesterol acetate tablets by using type II dissolution test apparatus with paddle to rotate at 50 rpm, 900 ml of 1% SLS was taken as dissolution media with temperature of 37±0.5°. The rank order of drug release of Megesterol acetate tablets with SSG and Crosspovidone is F6 > F7 > F3 > F8 > F4 > F5 > F2 > F1.

The rank order of drug release for the Megesterol acetate tablets with hydrotropic agents is F40 > F34 > F30 > F40. The formulation with the combination of three hydrotropic agents showed the better drug release.

Evaluation parameters:

The formulated Megesterol acetate tablets were evaluated for hardness, friability, weight variation, thickness, wetting time, disintegration time and drug content. The results were reported in the table no.25. In-vitro disintegration test was conducted for the Megesterol acetate tablets in 1% SLS as disintegrating medium in disintegration apparatus and the

disintegration time of the tablets was found to be less than 2 min and the wetting time was found to be 34-214 sec.

Comparison with marketed tablets:

The Megesterol acetate tablets formulated with solid dispersions and mixed hydrotropic technique showed greater drug release compared to the marketed formulation. The rank order of best formulation is

Tablets with hydrotropic agents > tablets with solid dispersion > marketed tablet

CHAPTER - 7

CONCLUSION

Megesterol acetate is a novel synthetic antineoplastic and progestational drug in the treatment of breast cancer. It is a new chemical entity, belongs to BCS class II, which exhibits low aqueous solubility and high membrane permeability that leads to poor bioavailability. Formulation was developed by using a novel mixed hydrotropic technique.

The summary and conclusions of investigations is as follows.

1. The present work was carried to design and development of Megesterol acetate immediate release tablets for the treatment of breast cancer.
2. The study demonstrates the preparation of fast dissolving Megesterol acetate tablets containing it's by using PEG 6000 as a carrier.
3. The carrier used in the solid dispersion and its concentration had significant affect in in-vitro dissolution of drug from solid dispersion.
4. The formulated tablets showed optimized upto 1:5 ratio, but the tablet showed dissolution efficiency within 1 hr 70% of drug release.
5. The study demonstrates the preparation of fast dissolving Megesterol acetate tablets containing its by using mixed hydrotropic technique with hydrotropic agents as urea, sodium benzoate, sodium acetate, sodium citrate.
6. It can be concluded that the concept of mixed hydrotropic solid dispersion is novel, safe and cost-effective technique for enhancing bioavailability of poorly water-soluble drugs by dissolving drug in nonionized form.
7. The magical enhancement in solubility of Megesterol acetate is clear indication of its 40% urea is the highest solubility among the four hydrotropic agents.

8. It can be concluded that these mixed hydrotropic agents are more soluble than individual hydrotropic agents. Finally the optimized mixed hydrotropic agent was dispersed equivalent weight of 20mg Megesterol acetate was taken and tablet was developed.
9. The formulated Megesterol acetate tablets were evaluated for hardness, friability, weight variation, thickness, wetting time, disintegration time and drug content. The disintegration time of the tablets was found to be less than 2 min and the wetting time was found to be 34-214 sec.
10. Drug release studies were performed for the tablets of of Megesterol acetate solid dispersion using hydrotropic agents. Drug release studies were conducted for the optimized formulations F16, F30, F34 and F40. The rank order of these four formulations based on maximum drug release is

    F40 (U+B+C) > F34 (A+B+C) > F30 (A+B) > F14 (B)

11. Comparative drug release studies were performed with the marketed Megesterol acetate tablet (Megrace). The rank order of the formulated Megesterol acetate tablets and Megrace based on maximum drug release is

    F40 (U+B+C) > Megrace > F34 (A+B+C) > F30 (A+B) > F14 (B)

    It can be concluded that Megesterol acetate solid dispersion using hydrotropic agents {F40 (U+B+C)} showed better drug release than the marketed formulation.
12. The developed Megesterol acetate tablets were able to treat breast cancer to produce onset of action of the drug with simple reasonable cost effective technique.

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